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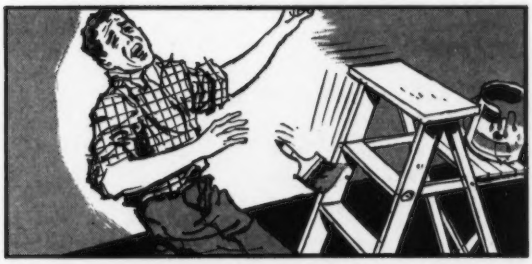

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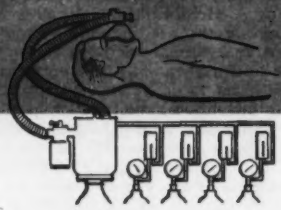

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A New Method for The Production of General Analgesia and Anaesthesia With A Description of The Apparatus Used

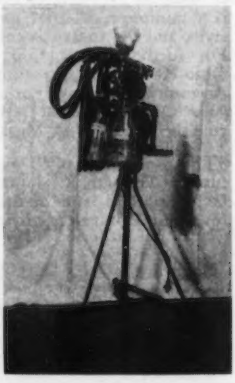
*By D. E. Jackson, M.D., Ph.D.

IN the following paragraphs there will be described a method for the production and maintenance of prolonged general analgesia or anaesthesia. The method involves a continuous process of rebreathing of the gaseous or volatized anaesthetics from which the exhaled carbon dioxide, etc., have been removed and to which oxygen is constantly added in proportions suitable to maintain the patient in a satisfactory condition.

So far, I have had an opportunity to try this method only on animals, but there seems to be good reason to expect that in man, results entirely comparable to those produced in animals may be readily obtainable.

Regnault and Rieset were probably the first to pass a current of oxygen into a small chamber in which an animal was confined for the purpose of analyzing the changes produced in the air by the respiration of the animal. They used a strong alkaline hydroxide solution to absorb the carbon dioxide output of the animal. Oxygen was added from a constant pressure reservoir. These principles have been used by practically all workers on respiratory metabolism since 1849.

In the present experiments I have utilized them not for the purpose of obtaining data regarding the metabolism of the animal, but with the object of maintaining conditions suitable for the normal respiration of the animal. At the same time, added to the respiratory medium are such quantities of gaseous or volatile anaesthetics as may be necessary to produce and maintain any desired and attainable degree of analgesia or anaesthesia, depending on the pharmacological properties of the substance administered.



A small electric motor operates an air pump. By means of a closed system of tubes and vessels, air may be kept continually circulating through the apparatus without either loss or gain of air except at the instance of the operator. Carbon dioxide is taken up by soda-lime while watery vapor is taken up by sulphuric acid. Oxygen must be replaced from the outside, and is injected from an ordinary commercial oxygen tank into the air circuit.

So far I have successfully used nitrous oxide, ether, chloroform, ethyl chloride, and the proprietary preparation "somnoform."

It is one of the basic principles of pharmacology that most anaesthetic substances which are administered through the lungs by inhalation are almost totally excreted again by exhalation from the lungs. By means of the constant circulation of the air within the machine, the exhaled anaesthetic is simply carried around, washed through the sulphuric acid and sodium hydrate solution and again returned to the animal for rebreathing.

It is thus seen that so long as no air is allowed to enter the machine from without and none is allowed to escape from within, the concentration of any given anaesthetic vapor within the machine and in the tissues of the animal must remain practically constant. Consequently the degree of anaesthesia should also remain constant.

The duration of anaesthesia by this method is usually limited only by the convenience or desire of the operator. With nitrous oxide, I have been easily able to keep dogs anaesthetized for periods of time extending up to a little more than five and one-half hours, and the animals are in excellent condition at the close of the anaesthesia. With ethyl chloride, one and one-half hours is the longest time I have so far tried to keep an animal anaesthetized. With ether or chloroform, the duration of the anaesthesia may be regulated entirely by the desire of the anaesthetist.

A more comprehensive condensed version of this "classic" prepared by William H. L. Dornette, M.D., appeared in the December '57 issue of our quarterly bulletin, "Anesthesia Items." Copies available upon request.

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Along about 1928, Dr. Heidbrink, in cooperation with Dr. John F. Lundy of the Mayo Clinic, designed the first gas machine to meet the specific requirements of surgical anaesthesia. Known as the Lundy-Rochester model, it permitted the administration of nitrous oxide, ethylene, oxygen and carbon dioxide. This new model measured the gases being administered with the use of the Bourdon Gauge and a flow orifice rather than just proportioning the gases.

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*The fourth "classic" on anaesthesia apparatus by Dr. D. E. Jackson apeared in the October, 1915 issue of the *Journal of Laboratory and Clinical Medicine.*

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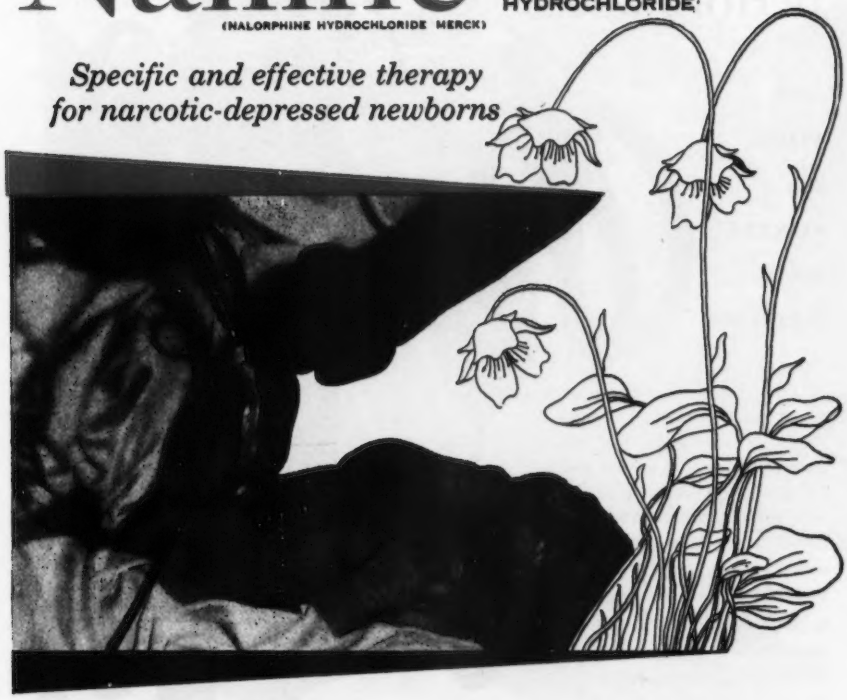

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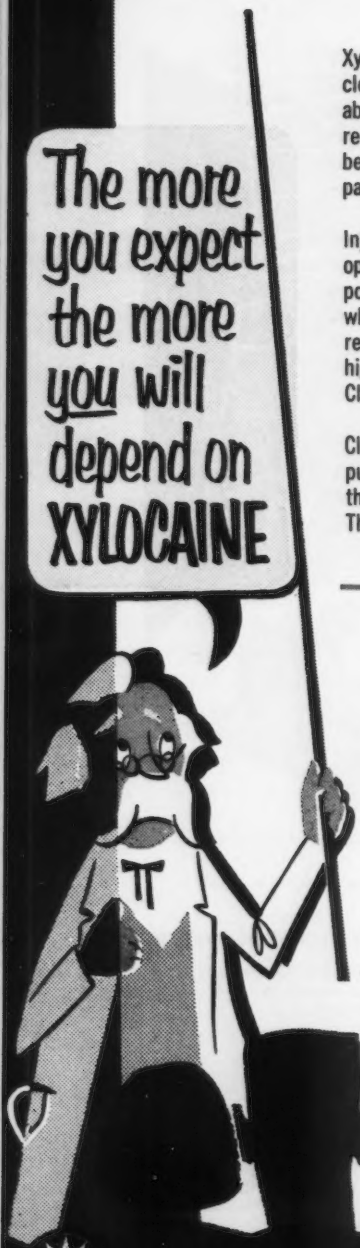

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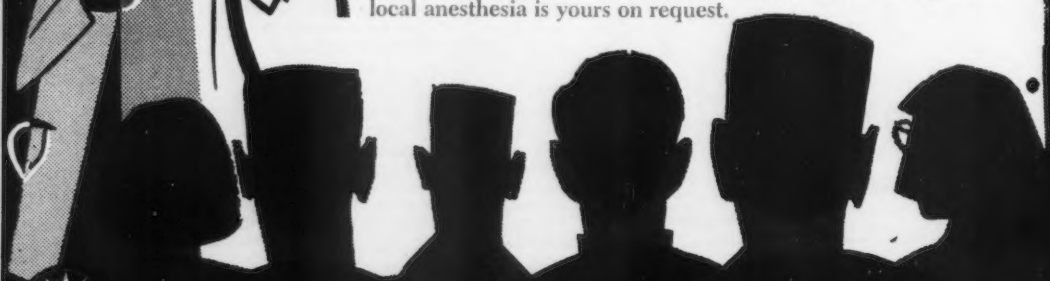

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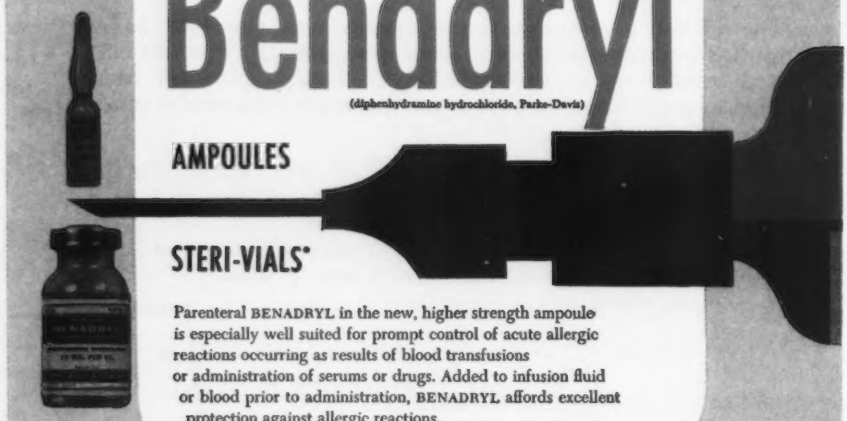

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DIFFICULTIES IN PAEDIATRIC ANAESTHESIA[1]

P. B. Percheson, M.D., F.R.C.P.(C), and John J. Carroll, M.D.[2]

PART I

General Considerations

It is a truism that the extremes of life are the most hazardous periods of our existence. Of the two extremes, the infant or child presents the more incalculable and inscrutable physiologic variations to challenge the skill and ingenuity of the anaesthetist.

The relative dearth of research in this field (13) is understandable when we consider that in infants and children we are dealing with such rapidly changing physiologic states that separate studies at different ages are necessary. We are repeatedly faced with difficulty in establishing the borderline between normality and abnormality. More attention must, therefore, be focused on the development of normal standards for this period when homeostasis is either not yet developed or so easily upset.

The anaesthetist must deal with paediatric patients in countless circumstances where speculation and clinical experience must take the place of knowledge and established fact. The life and welfare of these patients depend very largely on the anaesthetist's ability to exercise instantaneous and accurate clinical judgment, a judgment which must be tempered by the fact that the smaller the patient the shorter the road to disaster.

In order to minimize the difficulties in paediatric anaesthesia, it behooves us to acquire at least a working knowledge of the physiologic vacillations that the infant and child are likely to manifest. Consultation with the paediatrician and the internist is most desirable when perplexing electrolyte, fluid balance, circulatory, respiratory or metabolic upsets are present in the preoperative period. Moreover, the qualified paediatric surgeon (5) is probably better equipped to deal with the surgical problems of this age group. Preoperative consultation and correction of physiologic upsets will protect the anaesthetist against many of the anaesthetic difficulties which may arise; because once the patient is anaesthetized, these difficulties do not permit recourse to laboratory findings, consultation with a colleague, or to the policy of watchful waiting—so common in the other specialties.

Physiological Considerations in Paediatric Anaesthesia

Central Nervous System

The hypothalamic thermostat of the paediatric patient is unstable and has a tendency towards wide diurnal fluctuations. High temperatures increase the

[1]Department of Anaesthesia, Vancouver Grace and Burnaby General Hospitals, Vancouver British Columbia.

[2]An abridgement of this paper was presented at the Section of Anaesthesia, Canadian Medical Association, Edmonton, Alberta, June, 1957.

basal metabolism rate which, in turn, increases the oxygen requirements, the pulse rate, and the respiratory rate. Under these conditions, additional fluid loss and electrolyte disturbances will rapidly ensue.

In the presence of fever, the convulsive threshold of the child is readily triggered; especially if fluid and electrolyte disturbances, hypoxia and carbon dioxide excess co-exist. Thus it is wise to reduce fever by permitting heat loss through perspiration. Simple expedients, such as removing heavy bed-covers, ensuring good ventilation of the operating rooms and providing tepid sponge-baths, are usually effectual if central nervous disease and bacterial infection are ruled out or treated. In some instances, the use of aspirin, alcohol sponges and specific therapy may be required. Adequate oxygenation and elimination of CO_2, treatment of dehydration, correction of calcium and other electrolyte disturbances, and the use of anti-convulsive drugs in the premedication are additional measures in the control and prevention of convulsions during anaesthesia.

Respiratory System

The respirations of the paediatric patient (13), especially of the newborn infant, are subject to very broad, so-called "normal" fluctuations. A rhythmically irregular respiratory pattern of the Cheyne-Stokes type is observed frequently in both the premature and the full-term infant. Body plethysmograph studies recorded an average rate of 58 per minute in the newborn, but the extent of the range was found to vary from 31 to 114. The tidal volume varies from 5 to 12 cc. in the premature infant and from 10 to 25 cc. in the full-term infant. Alveolar ventilation—a complex resulting from the depth, rate and shape of the respiratory curve—is impossible to determine, even approximately, in the infant. Little can be concluded from arithmetical averages wherein so much variation occurs, and it is therefore impossible to estimate conclusively the oxygen and carbon dioxide values in this age group.

A very significant fact (13) is that in both premature and full-term infants, periodic breathing can usually be changed to regular breathing by the administration of oxygen. Thus, it has been postulated that since the foetal and newborn respiratory pattern shows the same irregularity that is known to occur with oxygen lack, and since this irregularity is readily corrected by the administration of oxygen, there must exist in this age group a tissue lack of oxygen. This has been attributed (13) to the characteristics of the foetal type of haemoglobin, which, though fully saturated, does not give up oxygen to the tissues readily. The improvement of the infant in oxygen-enriched atmosphere is apparently due to the greater concentration of oxygen in physical solution in the plasma.

These considerations emphasize the importance of employing some form of oxygen-enriched anaesthesia in infants. By the same token, some method of assisted ventilation which will increase the tidal volume from the normal 20 cc. to 100 cc. (14) is indispensable. We might therefore reiterate that high oxygen atmospheres and large tidal volumes are the sheet-anchors of paediatric anaesthesia. We must not forget that the technique employed must prevent CO_2 excess as this factor alone can cause sweating, tachycardia, rapid respirations, convulsions, and circulatory collapse.

Special Considerations of Ventilation and Circulation

Adequate ventilation and oxygenation are dependent upon good lung circulation. Both the blood volume and its distribution in the lungs and heart—the so-called lesser circulation—can be affected by many factors. Normally the latter amounts to about 20 to 30 per cent (4) of the total circulation. However, recent studies have demonstrated that approximately 80 per cent of the blood which pools in the legs when we assume the upright posture comes from the lungs and heart. Peripheral vasodilatation from anaesthetic drugs may effect a comparable redistribution. By the same token rapid blood loss may reduce the pulmonary blood volume by an amount equal to 50 per cent of the estimated blood loss. Thus, factors such as dehydration, vasodilatation, blood loss, and unphysiological postures during anaesthesia, may decrease the volume of the lesser circulation to a greater extent than that of the systemic circulation. In this situation, the pulmonary blood volume may be decreased to the critical point of inadequate venous return to the heart. A tachycardia may not compensate for this inadequacy; therefore cardiac output can become critically reduced. This can only be prevented by the control or treatment of all the conditions which deplete the pulmonary blood volume to the critical level.

Furthermore, when the blood volume of the lesser circulation becomes critically depleted, the blood in the lungs may be distributed unevenly. In the lateral posture which may be required for surgery, not only the blood but also the alveolar (15) gases may be distributed unevenly throughout the lung tissue. In this situation, shallow ventilation may distribute a greater amount of oxygen to areas of the lung where the circulation is poor, and relatively smaller amounts of oxygen to the areas of good lung circulation. This paradoxical situation can be either improved or corrected with high oxygen concentrations combined with the large tidal volume of assisted or controlled ventilation.

The Cardiovascular System

The pulse rate varies from 160 in the infant to 120 in the child (20). The blood pressure varies from 70/30 in the infant to approximately 80/40 in the child. Haemoglobin values range from 18 gm. (13) at birth to about 12 gm. at the end of one year. Under anaesthesia pulse-rate variations from 100 to 200 are quite frequent.

It is a sign of good anaesthesia when the infant's pulse rate is below 130 and the child's below 110. This, of course, only holds true when relaxation is adequate and the colour, respirations and blood pressure are optimum. Circulatory collapse as evidenced by tachycardia or bradycardia, imperceptible pulse, pallor or cyanosis, and respiratory difficulties, should be considered as complications of anaesthesia. This is especially true when blood loss, adrenal insufficiency or surgical factors cannot be incriminated.

Fluid and Electrolyte Balance

Body water comprises about 70 per cent of the total body weight of the infant (16). It is postulated that in the infant the extracellular fluid volume comprises from 25 to 50 per cent of their total body water, as compared to 20 per cent in

the adults. Thus, the adult whose extracellular fluid volume is about 14 litres ingests and excretes about 2 litres (equivalent to 1/7 of his extracellular fluid volume) daily. On the other hand, the infant whose extracellular fluid volume is about 2 litres ingests and excretes about 1 litre (equivalent to about ½ of its extracellular fluid volume) daily. It is obvious why deficits and abnormalities in fluid and electrolyte balance are at least seven times more likely to occur in the infant and child than in the adult.

Therefore the recognition and treatment of fluid and electrolyte deficits, when diarrhoea, vomiting, fever, trauma and decreased oral intake complicate the pre-operative period, are of paramount importance.

Some general principles in the approach to this problem are:

(*a*) Estimate the extent of dehydration that the disease process has inflicted on the child (1). This may be classified as mild, moderate or severe—amounting to 5, 10, or 15 per cent of body weight respectively—and will require the administration of proportionate amounts of oral or intravenous fluids. Approximately one-half of the quantity of fluids necessary to correct this existing dehydration is added to the maintenance requirements of the first day because this amount is sufficient to restore the extracellular (interstitial and plasma) fluid compartments.

(*b*) Where dehydration is mild to moderate, the total fluid requirements for the first day (the amount required to correct existing dehydration added to the 24-hour maintenance requirements) are administered over a 24-hour period. However, moderate to severe dehyration may necessitate more rapid rates of administration.

(*c*) When the child will tolerate it, oral administration of fluids is preferred and this can be continued until six hours before surgery.

(*d*) Blood, fluid and electrolyte losses from abdominal suction, etc., should be replaced as they occur.

(*e*) Shock should be treated with blood or plasma substitutes as indicated.

(*f*) After shock has been treated, it is safer to continue the intravenous with 5 per cent glucose or one-third normal saline in two-thirds 5 per cent glucose until clinical signs and laboratory data indicate the need of specific electrolytes in more concentrated solutions.

(*g*) Potassium solutions and sodium lactate should not be administered intravenously until shock is corrected and kidney function is re-established.

(*h*) An accurate fluid intake and output and weight chart should be kept and reviewed frequently (21).

In evaluating these patients, information must be obtained as regards recent diarrhoea, vomiting, excessive perspiration, fluid intake and output (1). A complete urinalysis and blood examination—including red cell count, haematocrit, N.P.N., sodium, potassium, chloride and CO_2 combining power—will help to elucidate the electrolyte and fluid deficits. Serum sodium can be estimated approximately be adding the figure 15 to the total of the serum chloride and the CO_2 combining power. All values must be in milliequivalents. It is well to remember that 10 per cent of body weight is equivalent to 15 per cent of body fluids.

Mild dehydration (1), as characterized by skin dryness, thirst and redness of the tongue and lips, usually indicates fluid deficit amounting to about 5 per cent of body weight. About 25 ml. per pound of body weight is required to correct this. However, as stated previously, only one-half of this amount is added to the maintenance fluid requirements as this is usually sufficient to replenish the extracellular fluid compartments. In these cases oral administration is preferred.

Moderate dehydration (1), as characterized by restlessness, irritability, sunken eye-balls and fontanelle, dryness of the lips and mouth, diminished skin turgor, cold extremities and an obviously ill patient, usually indicates fluid deficit amounting to 10 per cent of body weight—about 50 ml./lb. However, adequate replacement of extracellular fluids is accomplished by adding one-half of this amount to the maintenance requirements of the first day.

Severe dehydration (1) is characterized by a moribund infant. These patients are in shock and require immediate and adequate fluid therapy with blood, plasma substitutes or electrolyte solutions as indicated. A rapid rate of infusion (up to 15 ml./lb. in the first hour) may be required to raise and maintain their blood pressure. Their fluid deficit amounts to about 15 per cent of body weight or about 75 ml./lb. Although it may be necessary to replace only one-half of this, the volume of replacement is better judged by the clinical response of the patient.

Maintenance fluid requirements (1) to cover losses from urine and insensible perspiration, etc., will vary from 50 ml./lb. in the 5- to 20-lb. infant to about 30 ml./lb. in the 20- to 80-lb. child. Fever will increase these requirements by 8 per cent for each degree Fahrenheit that the temperature rises. Under normal circumstances, the maximal amount of fluid administered during surgery should not exceed 5 ml. lb. Even this amount may overload the 6- to 12-lb. age group. A vein should be cannulated in all infants requiring anything but the most minor surgery.

In the small infant whose 24-hour fluid requirements are about 300 ml., a two-way stop-cock should be incorporated into the intravenous set for the administration of anaesthetic drugs and medications during surgery. This will prevent cerebral or pulmonary oedema which might result if the drugs were otherwise injected into the intravenous tubing and the drip-rate necessarily increased to obtain their full effect.

The diagnosis of alkalosis or acidosis will depend on the correct interpretation of the history, character of the breathing, the urine and the blood pH (18). It is well to remember that the CO_2 combining power is an indirect measure of the blood pH. The true hydrogen ion concentration can be determined more accurately by measuring the alveolar CO_2 as this value corresponds to the tension of the carbon dioxide dissolved in the plasma.

Although the character of the breathing is our best clinical indicator of acidosis or alkalosis, one must not forget that a hyperpnoea of central origin may be compensated by the renal excretion of bicarbonate. In this situation, although the breathing is acidotic in character and the CO_2 combining power is low, the urine will be either neutral or alkaline and the arterial blood pH will be on the alkaline side, confirming the diagnosis of a compensated respiratory alkalosis rather than a metabolic acidosis.

Metabolic acidosis and alkalosis are usually associated with considerable fluid deficits (1). Alkalosis more often than acidosis is conductive to potassium and calcium deficits.

Mild acidosis may be corrected by the return of adequate kidney function, whereas, a CO_2 combining power below 12 milliequivalents associated with hyperpnoea will require the addition of appropriate amounts of one-sixth molar lactate solution as follows: 2 ml./lb. of body weight of one-sixth molar lactate

will raise the CO_2 combining power by 1 mEq. Enough of this solution should be administered to raise the CO_2 combining power to 20 mEq (1). (The normal CO_2 combining power is 27.5 mEq. or 55 volumes %.)

Alkalosis usually will be corrected by administration of normal saline. However, severe alkalosis with CO_2 values above 40 mEq., hypopnoea, cyanosis, abdominal distension and absence of bowel sounds may require the addition of potassium to effect clinical improvement. Potassium should not be given intravenously until an adequate flow of urine is established. It is a hazardous therapy unless abnormal losses have existed for 36 hours or more (1). The following formula is useful for estimating the therapeutic requirements: 1 mEq./lb. of body weight per 24 hours up to a total of 4 gm. (50 mEq.) in a concentration not greater than 30 mEq./L.

Tetany will usually respond to intravenous calcium gluconate (1); 5 to 10 ml. of this solution diluted with normal saline to 40 ml. can be administered over a period of 10 minutes as often as required.

Basic considerations for calculating the fluid requirements of a fairly common group of pediatric problems are as follows:

(*a*) The infant with pyloric stenosis will require a repair solution of one-third normal saline in two-thirds 5 per cent glucose in quantities up to a total of 75 cc. per pound of body weight over a 24-hour period.

(*b*) The infant with intestinal obstruction will require the judicious administration of normal saline or Ringer's lactate solution. It is safer to limit normal saline to approximately one-third of the calculated fluid requirements and to use code 8 (one-third normal saline in two-thirds 5 per cent glucose) or 5 per cent glucose solution for the remainder (1).

(*c*) In lower intestinal losses, and fever states with excessive perspiration and decreased fluid intake, a safer procedure is to administer code 8 until kidney function improves and blood N.P.N. starts to fall (1). After this, specific therapy for acidosis and potassium deficit can be considered. Shock may require blood or blood substitutes.

(*d*) As a general rule, saline should be used sparingly in the small infant (2 to 5 Kg.). Even code 8 contains about 4 times more saline than the infant's kidney can deal with normally.

Many serious situations can be avoided if at least a working knowledge of the fluid and electrolyte deficits of this age group is acquired. For instance, severe and prolonged lower intestinal losses, especially in the presence of fever and decreased oral intake, may result in dehydration, metabolic acidosis, potassium deficiency and poor kidney function. Improper therapy with normal saline per se will aggravate the condition and may precipitate convulsions. Normal saline increases the plasma chloride relatively more than the plasma sodium and thus imposes the strain of a dilutional acidosis in one's attempt to correct an already established metabolic acidosis. If this infant is then subjected to anaesthesia wherein CO_2 excess is not prevented, a further insult is added in the form of a respiratory acidosis superimposed on a metabolic acidosis which was already aggravated by a dilutional acidosis. In this situation, circulatory collapse, cardiac arrest or convulsions are almost inevitable.

Likewise, the infant with pyloric stenosis may develop metabolic alkalosis wherein poor kidney function, chloride, potassium and calcium deficits may manifest themselves clinically by apathy, hypotonia, absence of bowel sounds, respiratory weakness and cyanosis. Incorrect fluid therapy, such as 5 per cent glucose

exclusively, may help to correct the dehydration, but it does not restore the chloride, potassium and calcium deficits, and thus it aggravates the alkalosis.

Similarly, in this situation, anaesthesia and surgery are prone to precipitate disasters such as circulatory and respiratory collapse and convulsions. Several factors might contribute to this: hyperventilation during anaesthesia could aggravate the alkalosis and precipitate convulsions; potassium deficiency could increase the infant's susceptibility to tubo-curare; dehydration and under-nutrition might depress renal and liver functions and thus interfere with the detoxification and excretion of anaesthetic agents and succinylcholine-like relaxants.

Even if surgery proves to be uneventful, the continuing potassium losses in the postoperative period could precipitate weakness, apathy, intestinal ileus and circulatory collapse.

Therefore, we can avoid many serious difficulties in paediatric anaesthesia by concerning ourselves with the proper electrolyte and fluid therapy. Research in electrolyte and fluid balance is still in a state of dynamic darkness; therefore, paediatric consultation is not only desirable but often indispensable. In situations where consultation is unobtainable, the anaesthetist may be forced to deal with this problem in the preoperative preparation of these patients.

Endocrine Factors

Adrenal insufficiency—characterized by dehydration, failure to gain weight, vomiting and frequently diaorrhea—has been described in the literature (19). Children with this condition have been restored to good health by the administration of salt, DOCA and cortical extracts. Without this therapy, anaesthesia and surgery could be especially dangerous for these patients.

Other infants and children have had the benefits of cortisone therapy for its anti-inflammatory, anti-allergic or anti-shock properties (12). Therefore, conditions such as dermatitis, eye inflammations, asthma, rheumatic fever, fulminating septicaemia or staphylococcal pneumonitis may have necessitated the administration of cortical extracts.

It is generally recognized that all cortical extracts depress the pituitary secretion of ACTH (9). This may cause prolonged adrenal cortical depression which could precipitate circulatory collapse during stress situations such as anaesthesia and surgery. Since laboratory tests for adrenal cortical function may be equivocal, difficult to interpret, and often require several days to complete and assess, it is safer for us to assume that an infant or child who has been treated with cortical extracts in the past year is a potential victim of Addison's disease. They will require prophylactic cortisone administration before, during and after surgery. ACTH therapy is not as dependable as cortisone (9) because its use may take up to six days to restore adrenal cortical function. Even then, the anaesthetist cannot be certain that the adrenal cortex will respond adequately to the increased demands imposed upon it by surgery and anaesthesia. Without prophylactic steroid therapy, a shock-like picture may manifest itself before, during or after surgery. Pallor with circulatory collapse which is refractory to treatment with pressor drugs and intravenous solutions is characteristic of this type of complication.

In these patients, a history of previous steroid therapy plus laboratory evidence of hypoglycaemia, low blood sodium and chloride, high potassium values and a high total eosinophile count will establish the diagnosis of adrenal insufficiency (9). A poor response to pressor drugs and intravenous therapy should excite one's suspicions of this condition.

In the preparation of these patients for surgery, the intramuscular route of administration is preferred—even though the drug takes effect more slowly than when administered orally. The injection of cortisone or hydrocortisone assures us that the patient is getting the drug in the required amounts. A dose of 3 milligrams per pound of body weight is given—48 hours, 24 hours and 2 hours—before surgery. During surgery, intravenous hydrocortisone must be available for the treatment of any untoward event which might be attributed to an inadequate concentration of blood corticoids.

The large thymus as a cause of death under anaesthesia has been based on tradition rather than on fact (13). The more likely causes of death are overdosage of anaesthetic drugs, asphyxia and the lack of appreciation that the margin between good health and disaster is especially narrow in children.

PART II

Techniques in Paediatric Anaesthesia

Advances in most branches of anaesthesia have added new drugs and new techniques to our armamentarium. Many of these have been applied to the anaesthesia of infants and children with variable results. Difficulties in their application can only be overcome by devising equipment and methods of administration which are tolerated by the infant rather than subjecting this age group to machines and techniques which were devised for the adult. One often hears the sweeping statement that all of the methods and agents for anaesthesia can be used on the paediatric patient. This we believe to be true in principle but not in practice, because, as yet, advances in paediatric equipment and techniques have not kept pace with our enthusiasm to extend all of the modern concepts of anaesthesia to this age group. Thus the use of adult equipment in prolonged paediatric anaesthesia invariably leads to increased resistance, fatigue, and exhaustion of the respiratory system, CO_2 accumulation, sweating, fever, and circulatory collapse.

Open Ether with Oxygen

From the above deliberations it is not surprising that the technique of open drop ether with a flow of oxygen under the mask has been the workhorse not only of the occasional anaesthetist but also of many specialists. There is much to commend a technique where simplicity and minimal equipment prevail, and hypoxia can be avoided by the simple expedient of flowing 1 to 2 litres of oxygen under the mask (2).

However, there are many drawbacks with this technique:

(*a*) Prolonged surgery with this method tends to fatigue the infant whose inhalations must pass through several layers of gauze.

(*b*) The dead space under the mask which may amount to 50 to 100 ml. may result in the accumulation of CO_2.

(*c*) Minute to minute control of the unstable respiratory mechanism of the infant is not possible because the technique does not incorporate facilities for controlled or assisted respiration.

(*d*) In major abdominal surgery, control of relaxation is not always possible. Straining, cyanosis, tachycardia and increased secretions from anaesthesia which is too light will often give way to apnoea and circulatory collapse from anaesthesia which is too deep. This type of "see-saw" anaesthesia is exhausting not only to the patient but to the surgeon and anaesthetist as well.

(*e*) Prolonged administration of ether results in liver and kidney depression, haemoconcentration and increased incidence of postoperative depression and vomiting.

Despite these disadvantages, it is still satisfactory for short extra-abdominal operations in the relatively healthier infants and children. Divinyl ether (Vinethene) is considered safer than ethyl chloride for the induction of these patients (2).

In our quest for means to circumvent the drawbacks of open ether, many improvisations and techniques have been developed which attempt to supplement the art of anaesthesia with the more modern concept of balanced anaesthesia. This consists of administering small doses of several drugs for their specific and desirable effects. In addition, the horizons of paediatric surgery have widened considerably in the past few years and anaesthesia must cope with the increasing demands of this extending field. Therefore a short review of the advantages and disadvantages of the many other available anaesthetic techniques for paediatric surgery is in order.

Co_2 Absorption Technique

The standard closed-circuit machine is too cumbersome for infants and children because of the increased resistance and dead space. However, the introduction of the infant circle absorber has made closed-circuit anaesthesia feasible in this age group. It has placed cyclopropane at the disposal of the paediatric anaesthetist. The unit was devised with a view to eliminating dead space and respiratory resistance to the maximum degree. Although its efficiency for the newborn or very young infant may still be challenged, it has made safe closed-circuit anaesthesia available for the older infant and child.

The to-and-fro absorption technique was designed to fulfil the physiologic requirements of the infant and child. However, because of the tendency to overheating of the soda-lime canister there is a rise in body temperature, and the perspiration becomes profuse. This problem may persist despite frequent changes of soda-lime and canisters and the use of ice bags (2). One must remember that when the size of the canister greatly exceeds the child's tidal volume, the proximal soda-lime will exhaust rapidly and add considerably to the dead space. The unit is relatively cumbersome and its efficiency in the very young infant is questionable.

Semi-Closed or Partial-Rebreathing Technique

The semi-closed or partial-rebreathing technique owes its efficiency to the high flow of gases, part of which, along with a portion of the expirations, are blown off through the exhalation valve. By this means the CO_2 in the system is usually maintained near physiological levels. However, it has the following disadvant-

ages: (*a*) Large volumes of gases must be employed uneconomically (2). (*b*) Efficient utilization of cyclopropane and ether is relatively impossible. (*c*) It is not suitable for operations requiring deeper planes of anaesthesia unless supplemented by curare or nerve blocks. When cyclopropane or ether is used in this technique, the large flow of gases into the non-closed system dilutes the effects of these stronger agents, and even control of the planes of anaesthesia becomes very difficult. Without the addition of nerve blocks or curare this method does not provide the surgeon with the smooth and adequate relaxation required for abdominal surgery. Thus there is a sequence of light anaesthesia with its straining, pulse variations and increased secretions, alternating with profound anaesthesia with its depression bordering on complete collapse. This "see-saw" anaesthesia embarrasses all concerned—patient, surgeon, and anaesthetist.

Combined To-and-Fro or Circle (2) Absorption and Partial-Rebreathing Technique

The partial-rebreathing aspect of this technique utilizes a moderate flow of gases with a blow-off adjustment either through the conventional expiratory valve or through the distal end of the reservoir bag where a paper clip (2) can be attached to regulate the amount of escape. This is combined with the to-and-fro or circle absorption apparatus in order to gain the advantages of both techniques. This may be more apparent than real, because the high flow of gases still tends to make control of anaesthesia more difficult, and the to-and-fro absorption technique still tends to cause overheating.

The Insufflation Technique

The insufflation of ether and air into the infant's mouth is mentioned only to be condemned as unphysiological and exhausting. The method lacks control of both the drug concentration and the infant's respirations. The high flow may form a barrier to the spontaneous respiration and promote the accumulation of carbon dioxide.

A modification of this, known as the Ayre's technique, has been used to advantage for operations requiring little relaxation. The method is physiologically efficient because both the reservoir bag and the expiratory valve are discarded and the anaesthetic mixture is opened to the outside air. A flow of about two litres per minute enables the infant to inhale the anaesthetic mixture through one arm of the metal T-piece and outside air through the open-end arm. The entire exhalation of the infant is discharged through the open arm of the T-piece. There is practically no resistence with this system and some form of assisted respiration can be carried out by plugging the open arm of the T-piece intermittently. However, the method is not suitable for deep anaesthesia and was originally devised by Ayre for cleft-lip operations on children.

The Non-Rebreathing Technique

This method incorporates a non-rebreathing valve of low resistance which removes all the exhaled gases from the system. The elimination of resistance and CO_2 accumulation has made this technique very useful for anaesthesia in the

young infant. Assisted ventilation can be exercised by simultaneously squeezing the bag and plugging the valve with one's finger. The Fink modification of this valve automatically closes when the bag is squeezed. However, there are some disadvantages to the non-rebreathing technique. Induction must be accomplished by some other method (2) and intubation is essential for the adequate elimination of dead space. Furthermore, good relaxation is very difficult to achieve in the older infant and child. Therefore, "see-saw" anaesthesia is likely to prevail during abdominal surgery unless relaxants are injected intermittently.

Curare Techniques

The curare techniques in infants and children provide the anaesthetist with a medium for effecting and maintaining a minute to minute control of the respirations wherein the full tidal volumes of 100 cc. or more are utilized. In addition, the quantities of anaesthetic agents are reduced markedly and the relaxation provided facilitates the work of the surgeon. With this technique, endotracheal intubation, high oxygen concentrations and some method of assisting or controlling respirations are mandatory. All techniques which incorporate a source of oxygen and a rebreathing bag are suitable for curare administrtion. Thus "see-saw" anaesthesia can be avoided by the judicious administration of curare.

However, many authorities (5, 14) question the wisdom of injecting curare into infants and children. Stead (6) and Hodges (3) believe that the newborn infant tolerates tubo-curare poorly because it responds to the drug like a patient afflicted with myasthenia gravis. One hardly needs to be reminded of the profound and prolonged depression that tubo-curare inflicts on myasthenic patients. Conversely, suxamethonium, which is a bromide derivative of succinylcholine, appears to be well tolerated by the infant and child. Stead and Hodges reported that repeated administration of small dosages of suxamethonium—up to a total of 15 to 45 mg.—produced no incidence of prolonged apnoea in over 300 patients. They concluded that the infant tolerates suxamethonium at least twice as well as the adult, even though the infant's plasma cholinesterase level is comparatively lower. Stead used suxamethonium in dosages ranging from 0.3 to 0.8 mg./kg. of body weight and repeated these as often as required. Our experience with suxamethonium over the past four years has indicated that the drug can be both efficacious and relatively safe in children. We have used small quantities in infants and, to date, there have been no cases of prolonged apnoea or undue depression. However, we still view with trepidation repeated administrations of curare in the very young infant. Where clinical evidence of dehydration and electrolyte deficit is apparent, the drug may be dangerous and relaxation should be attempted by other methods. Although curare provides the anaesthetist with an effective means of controlling relaxation and ventilation, it does not block the autonomic reflexes. These may cause pulse-rate and circulatory disturbances which may prove deleterious to the infant.

Intubation Techniques

Endotracheal intubation is the *sine qua non* of good paediatric anaesthesia. It is indispensable to the proper utilization of the non-rebreathing, the Ayre's and all

curare techniques. Even the more efficient methods of ether administration such as the Flagg's can draw-over technique require intubation. Intubation either contributes to or confers more efficiency to all paediatric techniques because it practically eliminates the large dead space which might otherwise be present in the face mask. It facilitates the control of the airway and the tidal volumes of the patient. Specifically, safer planes of anaesthesia can be maintained during abdominal surgery without the fear of precipitating laryngospasm, stridor, reflex apnoea or other respiratory aberrations. Though some may argue that the incidence of infant morbidity may be increased by the occasional trauma of intubation, we feel that the safety and control established by the tube is a major factor in lowering surgical mortality. Because intubation makes anaesthesia safer, more physiological, more controllable, more predictable and more reversible, the narrow road from apparent good health to disaster can be better charted in the intubated infant and child.

Block Anaesthesia

Block anaesthesia such as spinal, epidural and regional infiltration can be utilized to great advantage in infants and children. Difficulties in controlling the patient, establishing dosages and maintaining the height and duration of the block have probably resulted in lack of enthusiasm for these procedures. With regards to epidural block, it has been our experience that relatively larger dosages of anaesthetic agents, far beyond those suggested by the stature and body weight, are required in the paediatric patient. Hunter (8) refers to this problem in the administration of spinal anaesthesia to children. It seems that because of the highly vascular piamater, the drug is rapidly absorbed into the blood stream, leaving a smaller quantity to become fixed to the nerve roots. This tendency to rapid absorption probably prevails in the epidural space of infants and children.

Since spinal and epidural anaesthesia is next to impossible to execute in the uncooperative squirming child, we believe that these youngsters should be put to sleep prior to block administration. A vein should be cannulated if an intravenous drip is not already running. In this way, quiet and controllable conditions facilitate block procedures, whereas the intravenous serves as a safeguard against complications which might arise either during or after the block. In the toxic and dehydrated child, block anaesthesia may be hazardous unless pressor drugs, oxygen and intravenous therapy are used judiciously. Under these conditions it may be the anaesthetic of choice (11), because once the spinal or epidural is established "see-saw" anaesthesia is usually prevented. Pulse-rate, respiratory, temperature, electrolyte and fluid disturbances are better controlled by regional anaesthesia. Nitrous-oxide and oxygen mixtures are usually sufficient to keep the child asleep throughout an operation performed with block anaesthesia. Admittedly, block administration may be more difficult to execute than the surgical operation. However, under controlled conditions, the task is less tedious and the results rewarding to the patient, surgeon, and anaesthetist.

We have found that an infant will require at least 6 ml. of 1 per cent Xylocaine to effect an epidural block, while a 6- to 8-year-old child may require 8 to 12 ml. of 2 per cent Xylocaine for the same procedure. The addition of 1-2 mg. of

neosynephrine to the aqueous Xylocaine tends to prolong the duration of the block and prevent undue drops in blood pressure. We deplore the use of Xylocaine-epinephrine solutions because epinephrine will increase the infant's pulse rate and will preclude the administration of cyclopropane or trichlorethylene if the block wears off too soon or proves inadequate. Also, there is some evidence (17) that because of the acid pH necessary to keep the epinephrine stable in the stock Xylocaine-epinephrine solutions, the mixture can release neurotoxic metallic ions from plated-metal syringes and receptacles.

Where spinal or epidural anaesthesia is not feasible, we believe that regional infiltration is a valuable adjunct to light inhalation anaesthesia.

Special Considerations in the Premedication of the Paediatric Patient

It is our contention that proper premedication of the paediatric patient is a variable factor which depends upon the technique and the agent that is to be used for anaesthesia. When the technique does not routinely incorporate measures for assisting or controlling respirations, then minimal depressant drugs and maximal doses of drying agent are indicated. In comparable doses scopolamine is a better drying agent and longer lasting than atropine. Scopolamine has a central amnesic action which potentiates the hypnotic properties of opiates and barbiturates. Atropine, on the other hand, is a good drying agent when large doses are administered about one-half hour before the operation. However, larger doses stimulate the central nervous system and thus increase metabolism and oxygen requirements. We prefer either morphine or meperidine (Demerol) as preoperative sedatives in the older infant and child. We have found that the phenothiazine drug promethazine (Phenergan of Poulenc Limited) has desirable preoperative properties. There is a growing body of authorities (7) who believe that the phenothiazine drugs exert their depressant action on the reticular activating system of the brain stem. They consider these so-called reticular formations to be centres of prodigious synaptic activity where autonomic, sensory and motor impulses are collected and integrated before being relayed to the thalamus and cortex. Penfield (10) has shown that the cortex merely acts as a way-station for sensory impulses which arise in the periphery and converge on the brain stem. Likewise, the cortex merely acts as a way-station for motor impulses which are integrated in the reticular formations and destined to reach the muscles through the cortico-spinal tracts. He demonstrated that pain pathways leaving the brain stem make no detour to the cortex but pass directly to the thalamus and back again through the reticular formations. Because destruction of the upper regions of the brain stem produces somnolence and unconsciousness, the state of arousal and consciousness is apparently the result of reticular formation activity and its effect upon the cortex. Thus we concur with Penfield, who maintains that the main target of premedication should be this rendezvous of psyche and soma—the reticular formations—and not the cortex. To accomplish this, we use promethazine in doses of approximately 1 mg. for every 3 lbs. of body weight. This has resulted in effecting a more quiescent and tranquil patient in whom induction of anaesthesia is facilitated, and maintenance is accomplished with weaker and less toxic

anaesthetic mixtures. Promethazine offers many other advantages (7) in paediatric premedication: (*a*)It depresses vagal and sympathetic reflexes and thus stabilizes the cardiovascular system. (*b*) It helps to protect the respiratory system against reflex disturbances such as may occur during abdominal surgery. (*c*) It potentiates the drying effect of atropine and scopolamine (*d*) It has appreciable anti-emetic, anti-convulsive and anti-pyretic properties. (*e*) It has no appreciable effort on blood pressure and does not depress respiration. All of these factors are most desirable targets to aim for in the paediatric patient.

Our premedication routine consists of giving only scopolamine and promethazine to infants weighing less than 20 lb. Scopolamine is used in doses varying from 0.1 mg. in the smaller infants to 0.14 mg. in those weighing 20 lb., and promethazine is administered in doses of 1 mg. for every 3 lb. of body weight. In children weighing more than 20 lb., Demerol to the extent of 0.5 mg./lb. or morphine to the extent of 0.5 mg. to 0.7 mg. for every 10 lb. of body weight, is added to the prescribed dosages of scopolamine and promethazine. Therefore, a 30-lb. child may receive 0.15 mg. of scopolamine (gr. 1/400) plus 10 mg. of promethazine and either 2.0 mg. of morphine or 15.0 mg. of Demerol. The amounts of Demerol and morphine are reduced by about 25 per cent when the open-ether technique is contemplated.

Induction of the Paediatric Patient

The hazards of vomiting, silent regurgitation and air-swallowing can be practically eliminated by passing a gastric tube in all infants before the induction of anaesthesia. Since crying practically doubles the metabolism and oxygen requirements (13), and wakefulness without crying causes a 15 per cent increase in these factors, it is certainly of great benefit to the child if a smooth and rapid induction is carried out. We believe that the addition of promethazine to the premedication has facilitated the induction appreciably. Some of us prefer rapid intravenous induction with thiopentone in dosages of 2 mg./lb. combined with 15 to 20 mg. of the cation of suxamethonium. Thiopentone and suxamethonium are miscible without precipitation and can be administered from one syringe. In the 2- to 5-year-old child, suxamethonium in dosages of less than 15 to 20 mg. may not relax the glottis sufficiently to permit intubation. Therefore, 15 to 20 mg. of relaxant is used routinely in this age group. Under the age of 2 years, the veins may be more difficult to cannulate, therefore, cyclopropane induction is usually preferred. However, if an intravenous is already established, suxamethonium is administered in dosages from ¼ to ½ mg./lb. For this reason, all the patients who are induced with the thiopentone-suxamethonium technique and most of the patients who are induced with cyclopropane are intubated.

Maintenance of Anaesthesia

For most of the extra-peritoneal surgery, including tonsillectomies, we prefer nitrous oxide plus oxygen and trichlorethylene mixtures in a semi-closed or non-rebreathing system. This mixture is non-explosive and permits the use of cautery and X-ray during surgery. For some of the short fracture procedures the further addition of curare or thiopentene may be required occasionally. For abdominal

surgery, some of us prefer block procedures in conjunction with a light inhalational anaesthetic. Others use either cyclopropane in an infant CO_2 absorption system, or a non-rebreathing ether technique with small supplements of curare.

Summary and Conclusions

The most serious difficulties in paediatric anaesthesia may not be directly related to the agents, techniques and abilities of the anaesthetist, as the sick child may be debilitated by electrolyte and fluid deficits of such magnitude that respiratory and circulatory collapse will occur even in the best of hands. More time, attention and care must be given to the clinical evaluation and correction of these factors in order to prevent disaster. It may take up to 24 hours to properly and adequately correct dehydration, acid-base disturbances, potassium loss, and calcium deficits. In these situations the paediatrician may be indispensable. The anaesthetist must have at least a working knowledge of these problems in order to be able to cope with them adequately in situations where paediatric or internist consultation is not available.

When electrolyte and fluid deficits have been corrected, difficulties can be better avoided by choosing methods, agents and anaesthetic techniques which are least disturbing to the labile respiratory, circulatory, metabolic and temperature regulating systems of the infant and child. In this respect, premedication must aim not only at reducing secretions, metabolism and oxygen requirements, but also at achieving a tranquil co-operative patient in whom vagal, sympathetic, motor and sensory pathways have been centrally obtunded. Likewise, maintenance of anaesthesia should incorporate versatility to the extent of permitting adequate oxygen, control of respiration, and, sufficient relaxation without undue circulatory and respiratory depression. We believe that the use of phenothiazine drugs in the premedication, and the administration of "controlled" blocks for the maintenance of anaesthesia may help to solve some of these difficulties.

Acknowledgments

We wish to acknowledge the contributions and advice of our associates—Drs. J. A. McNab, J. W. Dennis and A. C. Blair—in the preparation of this article. A special thanks to Dr. E. E. McCoy, Paediatrician at Burnaby General Hospital, for his constructive criticism on paediatric fluid and electrolyte problems.

Résumé

En anesthésie pédiâtrique, les plus sérieuses difficultés peuvent bien ne pas être d'ordre technique ou ne pas être attribuables aux agents ou à la dextérité de l'anesthésiste, si le petit malade est dans un tel déséquilibre hydrique et électrolytique qu'un collapse respiratoire et circulatoire peut survenir même dans les mains les plus habiles. Pour éviter un désastre, l'évaluation clinique et la correction de ces facteurs requièrent plus de temps, d'attention et de soin. Pour corriger adéquatement la déshydratation, le déséquilibre acidebase, les pertes de potassium

et le déficit de calcium, il peut être nécessaire de prendre 24 heures. Dans de telles circonstances, le pédiâtre peut devenir indispensable. L'anesthésiste doit être assez familier avec ces problèmes pour pouvoir, s'il est impossible de consulter un pédiâtre ou un interniste, prendre la situation en main et permettre l'intervention.

Une fois l'équilibre hydrique et électrolytique rétabli, il sera plus facile de contourner les difficultés inhérentes au choix des méthodes, des agents et des techniques anesthésiques qui affecteront le moins les systèmes régulateurs labiles de la respiration, de la circulation, de la température et du métabolisme de l'enfant ou du poupon. A ce sujet, la prémédication ne doit pas viser qu'à réduire les sécrétions, abaisser le métabolisme et diminuer les besoins d'oxygène, mais elle doit tendre également à présenter à la salle d'opération un malade calme, coopérant dont l'activité nerveuse est ralentie, activité vagale, sympathique, sensitivo-sensorielle et motrice. Il en est ainsi du maintien de l'anesthésie: il doit être possible de faire des variations qui permettent une oxygénation adéquate, un contrôle de la respiration et un relâchement musculaire suffisant tout en évitant une dépression respiratoire et circulatoire nuisible. Nous avons la conviction que l'emploi des dérivés de la phénothiazine dans la prémédication et la pratique de blocages circonscrits pour le maintien de l'anesthésie peuvent aider à résoudre quelques-unes de ces difficultés.

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ANAESTHESIA FOR SURGICAL REPAIR OF OESOPHAGEAL ATRESIA AND TRACHEO-OESOPHAGEAL FISTULA

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OESOPHAGEAL ATRESIA is a congenital anomaly found in the newborn requiring surgical correction as a life-saving measure. This anomaly is most frequently associated with tracheo-oesophageal fistula which connects the trachea to the oesophagus, either above or below the atretic portion. Tracheo-oesophageal fistula may occur without oesophageal atresia. Aspiration pneumonia frequently occurs in patients with this direct communication between the oesophagus and trachea. An early diagnosis, prior to feeding, will allow surgical correction before dehydration occurs and will reduce the amount of tracheo-bronchial contamination. This is imperative if the survival rate for this anomaly is to be improved. An early diagnosis can be easily accomplished in the delivery room. It is necessary for the obstetrician, anaesthesiologist, and those concerned with infant resuscitation, to be constantly aware of this anomaly. It occurs in about one in twenty five hundred births. Apgar (1) has advocated the routine passing of a catheter into the stomach of the newborn to show immediately if the oesophagus is patent. Obstruction to the passage is presumptive evidence of oesophageal atresia. This procedure repeated under fluoroscopy may be all that is necessary to establish the diagnosis.

Numerous techniques for the conduct of anaesthesia have been advocated for the surgical correction of this anomaly. Zindler and Deming (2) intubate the patient awake and use cyclopropane in the semi-open technique with a non-rebreathing valve. The respiration of the infant is controlled. They emphasize careful tracheal aspiration during surgery and in the postoperative period. Wilton (3) advocates the use of a T-piece connected to an endotracheal tube. Respiration is managed by intermittently occluding one limb of the T-piece while a continuous flow of fresh gases enters the other limb. Payne (4) injects thiopental and d-tubocurare into an intravenous cutdown. Respiration is controlled using nitrous oxide–oxygen in a semi-closed system with an infant carbon dioxide absorber. He emphasizes that infant breathing is mainly diaphragmatic which tends to put a variable degree of strain on the lower segment of the oesophagus. Local anaesthesia is unsatisfactory for the surgical repair of this anomaly owing to the tension placed on the oesophagus as a result of coughing and straining of the patient.

There still remains considerable disagreement among anaesthesiologists and surgeons in regard to endotracheal intubation in these patients. Those who oppose it feel that intubation may produce laryngeal oedema. Swenson (5) advocates the adminstration of cyclopropane by a tight-fitting mask without endotracheal intubation. Haight and Towsley (6), in 1943, reported the first successful primary correction of oesophageal atresia and tracheo-oesophageal fistula. They used local anaesthesia for the first part of the operation. Open-drop

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ether was given during the anastomosis to obtain quieter working conditions. This same anaesthetic procedure was used at Indiana University prior to 1948.

Technique

These patients usually enter the hospital with an elevated temperature and marked dehydration. Surgery should not be performed until the patient has been given antibiotics and hydrated. An intravenous cutdown with a polyethylene tube, preferably at the ankle vein, should be performed prior to surgery.

Prior to 1948, all of these patients at the Indiana University Hospitals received local infiltration with procaine until the chest was opened and the dissection was completed. Open-drop ether was given while the anastomosis was done to produce a quieter operating field. Since 1948, endotracheal intubation and general anaesthesia has been used. Intubation is accomplished while the patient is awake or after anaesthesia is induced with open drop ether. The size of the tube has varied between a 14 French and a 16 French catheter.

Controlled respiration is carried out through the entire procedure in order to ensure adequate ventilation and prevent diaphragmatic movements which place a tension on the lower oesophageal segment. Controlled respiration also allows the patient to be carried in a lighter plane of anaesthesia. An infant 90-gram to-and-fro canister is connected to the endotracheal tube. A 500 cc. bag is attached to the canister and the tail of the bag is used for escape of gas. The gas inflow is between the endotracheal tube and the canister. With this setup, the anaesthesiologist can control respiration with one hand, leaving the other hand free for the many things that come up during this type of surgery. This type of anaesthesia can be managed by one person if the procedure is well planned in advance.

Non-rebreathing valves have been used but have the disadvantage of constantly requiring both hands for the control of respiration. Fink's modification of the Stephen-Slater valve has obviated this difficulty. This valve has been used satisfactorily on recent patients having this type of surgery. The maintenance of anaesthesia consists of nitrous oxide and oxygen with a total flow of three to four litres. The oxygen concentration is kept between 30 and 50 per cent. Ether is added as required. Recently, intramuscular succinylcholine in 10 mg. doses has been given as required to produce quiet working conditions and prevent deep planes of ether anaesthesia.

The trachea should be aspirated frequently to prevent the accumulation of secretions. Premedication with atropine has made no noticeable change in secretions of these patients and is, therefore, not used.

Blood loss is determined by the measurement of blood in the suction bottle and the weighing of sponges. The loss is replaced as accurately as possible.

It has been found helpful to monitor the heart action with an electrocardiophone or an electrocardiograph with or without an oscilloscope.

Postoperatively, the infant is placed in humidified oxygen. Frequent aspirations are performed to keep the pharynx free of secretions. The day after surgery, a gastrostomy is done under open-drop anaesthesia.

Case Analysis

An analysis of the cases done at Indiana University from 1940 to 1956 is summarized in Table I. There were a total of 86 newborn infants with this anomaly operated during this period. These included oesophageal atresia with tracheo-oesophageal fistula, oesophageal atresia without tracheo-oesophageal fistula, and tracheo-oesophageal fistula alone. The older patients are not included in this report since the operative risk is hardly the same. Two patients, one and three years of age respectively, had tracheo-oesophageal fistula alone, and both made uneventful recoveries following surgery.

TABLE I

	Without tube (1940-8)		With tube (1948-56)	
	No.	%	No.	%
Lived	2	11.7	40	58
Died	15	88.3	29	42
During surgery	2	11.7	0	0
During first 48 hours	8	47	15	21.8
Total no. of patients	17		69	

The over-all mortality in this group was 51 per cent. A comparison of the mortality is listed in two groups since a radical change was made in the anaesthesia management in 1948. Of the 17 patients operated prior to 1948 15 died, whereas only 29 out of 69 patients failed to survive after 1948.

Although the anaesthesia management was of great importance in the increased survival rate, other factors played an important part. Early diagnosis, increased surgical experience, and better preoperative and postoperative care are but a few of the factors which have helped to lower the mortality rate in these patients.

There were 8 deaths in the 1940–8 group during the first 48 hours postoperatively, and 2 patients died on the operating table. The early death rate for this group was 47 per cent. The second group, since 1948, shows 15 early postoperative deaths giving a mortality rate of 21.8 per cent. It is thought that the early mortality rate may be a more accurate index of the effect of improved anaesthetic management.

The three types of anomalies are compared in Table II. The most favourable prognosis is in the group having tracheo-oesophageal fistula without atresia of

TABLE II

Oesophageal Anomalies

	No. of cases	Percentage of total	No. died	Percentage
Atresia with fistula	75	87	37	49
Fistula	7	8	1	14
Atresia without fistula	5	6	4	80
Total	87		42	

oesophagus. There were seven of these patients operated with only one failing to survive. Patients having oesophageal atresia without a fistula had the highest mortality rate with only one of five surviving the operation. In these patients, there is insufficient oesophagus to allow for a primary repair. The reconstruction requires more extensive surgery. The most common anomaly is oesophageal atresia associated with tracheo-oesophageal fistula. Thirty-seven of seventy-five patients failed to survive the operation giving a mortality rate of 51 per cent over the entire period.

Other anomalies in addition to oesophageal atresia occurred in 23 patients and are shown in Table III. Imperforate anus was the most common anomaly in this group and occurred in 11 patients. Anomalies of the heart and great vessels were found in 7 patients. Other anomalies included duodenal atresia, absence of the kidney, skeletal deformities, and hypospadius. In this group 8 patients failed to survive, giving a mortality rate of 35 per cent.

TABLE III

	Lived	Died	Total
Heart and great vessels	4	3	7
Imperforate anus	8	3	11
Absence of kidney	0	1	1
Skeletal deformities	1	0	1
Haemangioma	1	0	1
Duodenal atresia	0	1	1
Hypospadius	1	0	1
TOTAL	15	8	23

Respiratory complications were listed as the chief cause of death. These complications were due to aspiration, atelectasis, pneumonitis with focal degeneration, pulmonary oedema, pneumothorax, or disruption of the anastomosis. A critical analysis of all patients failing to survive shows that there was only one death directly due to anaesthesia. This patient was given 1 mg. of curare during ether anaesthesia. Spontaneous respirations never returned, although ventilation was maintained manually for 24 hours before the patient expired. A suture was placed through the tip of the tube in one case. Only slight traction was necessary to remove the tube. The suture was seen by bronchoscopy over the site of the fistula. There were no laryngeal complications and, to this date, none has required tracheotomy.

SUMMARY

There appears to be no question about the advantages of endotracheal intubation in the administration of anaesthesia for the repair of oesophageal atresia and tracheo-oesophageal fistula. Controlled respirations provide ideal working conditions when every advantage is needed for working in a small space. Ventilation is maintained even though there may be severe pulmonary disease. Minimal anaesthesia is required. Laryngeal oedema cannot be held as a deterrent with all the advantages to be gained. Finally, the anaesthesiologist is in a position to aid in the early diagnosis.

Résumé

De nombreuses techniques ont été préconisées pour pratiquer l'anesthésie en vue de la correction chirurgicale de l'atrésie de l'œsophage et de la fistule trachéo-œsophagienne. Les anesthésiologistes et les chirurgiens ne sont pas encore d'accord sur les avantages qu'il y aurait à pratiquer chez ces malades l'intubation endotrachéale. Ceux qui s'opposent à l'intubation donnent pour raison que l'intubation peut provoquer de l'œdème laryngé.

Les auteurs ont analysé les résultats de ces opérations pratiquées chez deux groupes de malades traités pour de telles anomalies dans les hôpitaux universitaires de l'Indiana. Dix-sept de ces malades ont été opérés entre les années 1940 et 1948 et seulement deux ont survécu, ce qui fait un taux de mortalité de 88.3%. Chez ces malades, on avait fait une infiltration à la procaïne jusqu'à l'ouverture du thorax et, une fois la dissection terminée, on donnait de l'éther en goutte à goutte duant l'anastomose. De 1948 à 1956, on a intubé tous les malades et pratiqué de la respiration contrôlée. Durant ces années, 69 malades ont été opérés dont 29 sont morts soit un taux de mortalité de 42%.

La principale cause de la mort a été les complications pulmonaires. Une analyse critique de ces mortalités démontre qu'il n'y a eu qu'une mort attribuable directement à l'anesthésie.

Il ressort que les avantages de l'intubation endotrachéale sont évidents au cours de l'anesthésie en vue de la réparation de l'atrésie de l'œsophage et de la fistule trachéo-œsophagienne. La respiration contrôlée procure des conditions de travail idéales au moment où on a besoin de toutes les facilités pour travailler dans un petit espace. Il est possible de conserver une ventilation adéquate en dépit parfois de malades pulmonaires sérieuses. Un minimum d'anesthésie est nécessaire. L'œdème laryngé ne peut pas être considéré comme un obstacle quand on songe à tous les avantages que procure l'intubation.

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STUDIES ON THE CARDIOVASCULAR ACTIONS OF CHLORPROMAZINE

III. EFFECTS ON CEREBRAL BLOOD FLOW, BLOOD PRESSURE, AND ELECTROCORTICOGRAM, AS RECORDED SIMULTANEOUSLY[1]

A. ROMAGNOLI and K. I. MELVILLE[2]

ALTHOUGH CHLORPROMAZINE is primarily employed as a central nervous system depressant drug, Lehmann and Hanrahan (1) early reported convulsive seizures as a side-effect of therapy in psychiatric patients. Using the "cerveau isolé," Das, Dasgupta and Werner (2) also observed increased electrical activity following injections of the drug. Indeed, in one case of chlorpromazine poisoning definite convulsions have been reported (3). Schlichther *et al.* (4) have also more recently stated that as high as 52.4 per cent of the patients under intensive chlorpromazine therapy show convulsive seizures.

Preston (5), using cats, recorded both depression and stimulation of the central nervous system function, and suggested that "chlorpromazine is a neuronal stimulant and that the amygdala is particularly sensitive to this drug." Indeed, this author postulates that the "tranquillizing" effects of chlorpromazine might be due to the increased electrical activity of the amygdala.

Berger *et al.* (6) have reported that in curarized cats artificially respired recordings of electrical changes from cortical and intercortical structures showed that "chlorpromazine at a dose of 1 to 15 mg./kg. produced irregular slowing in the cerebral cortex, with outbursts of 7 to 10 cycles/sec. of activity and occasionally slow waves of 2 to 3 cycles/sec." Margolis (7) has also concluded that in man "convulsions are far from uncommon in intensive chlorpromazine therapy."

On the contrary, Winkelman (8) observed that chlorpromazine potentiates the sedative actions of anti-convulsant drugs, and Goldman (9) could observe no evidence of seizures in 500 patients receiving up to 2.4 gm. daily. Kelly and Lawrence (10) have also reported that chlorpromazine decreases seizures in clinical and experimental tetanus, and Thibault (11) treated successfully a patient with severe postoperative convulsions with the so-called "lytic cocktail."

Lehmann has further postulated that the convulsions observed after chlorpromazine might be due to hypoxia of the brain following syncopal attacks due to orthostatic hypotension (12), but the problem has been somewhat obscured by the fact that in some patients it was noted that there had been a previous history of convulsive seizures (1).

In view of the above observations and in connection with other studies in this laboratory concerning the general cardiovascular actions of chlorpromazine (13, 14) it was of interest to investigate its influence upon the cerebral blood flow, blood pressure and associated electrocorticogram, as recorded simultaneously.

[1]Supported in part by grants from Poulenc Ltd., Montreal.

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In connection with these studies a number of similar experiments were also performed using diethazine (Diparcol). Jenkner and Lechner (16) have reported that the electrical abnormalities associated with cerebral trauma were normalized by administration of Diparcol. There are no other studies in the literature on this question so far as we are aware.

Methods

Dogs were used. In general, the animals were first etherized and artificial respiration instituted and maintained throughout all the experiments. The operative procedure consisted of a mid-line incision extending from the base of the nose to the occipital protuberance. The juncture of the sagittal and coronal sutures was exposed. Three small (4 mm. diameter) holes were trephined in the skull in such a manner as to form a triangular area, the middle of which was located approximately 1 cm. lateral and 1 cm. posterior, to the previously identified junction of the sutures. After this procedure was completed, the animals were curarized with succinylcholine (1 mg./cc.) by continuous intravenous drip, the total dose ranging from 200 mg. to 500 mg. The cerebral blood flow (C.B.F.) was measured by an indirect method, using the principle described by Ludwig (15) modified to record the temperature changes, after suitable calibration. A diagram of the electrical arrangement employed is shown in Figure 1. The

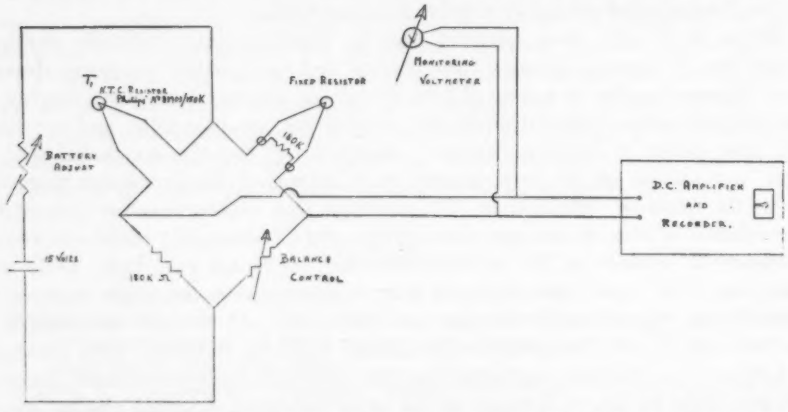


Figure 1. Diagram of bridge for measuring temperature variations due to changes in the cerebral blood flow (C.B.F.). The output of the bridge varies with the temperature at T_1, as recorded by the N.T.C. Resistor.

temperature changes of the underlying cerebral cortex are picked up by a N.T.C. Resistor.[3] The tip of the resistor (1 mm. in diameter) was placed through the middle orifice in the skull and directly in contact with the exposed cerebral cortex of the lateral gyrus on the left side. The electrocorticogram, referred to as E.E.G., was recorded from the same area of the brain by two fine platinum electrodes

[3]Negative Temperature Coefficient Resistor kindly supplied by the N. V. Phillips' Gleeinlampenfabrieken, Eindoven, Netherlands.

(0.5 mm. in diameter), inserted through the two orifices on either side of the resistor, approximately 1 cm. apart—the tip of the electrodes being placed on the unopened dura mater, in order to avoid unnecessary damage to the brain and excessive leakage of the cerebrospinal fluid.

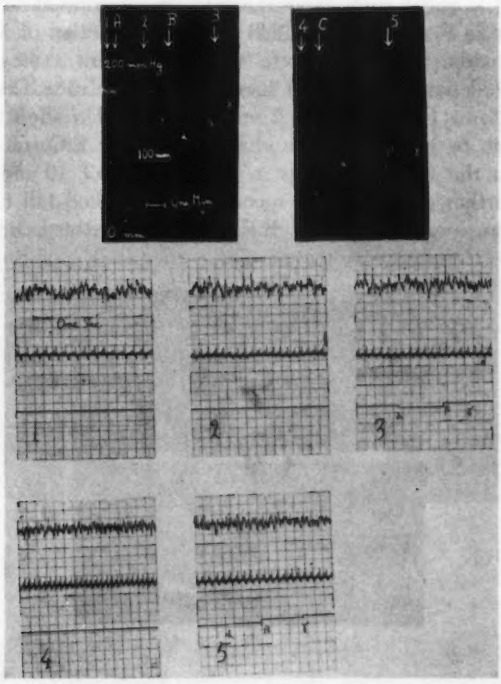


FIGURE 2. Dog, male, 14.0 kg. *Above*, kymographic blood pressure records—an interval of 10 minutes elapsed between each section, during which an additional dose of 10 mg./kg. of chlorpromazine was injected. At A, chlorpromazine (5 mg./kg.) and at both B and C. chlorpromazine (10 mg./kg.) were injected. *Below*, sections of E.E.G., E.C.G. and C.B.F. records taken at nos. 1 to 5, as marked on the kymographic records—on nos. 3 and 5α, β and γ, corresponding to points so marked on the blood pressure record above.

Both the E.E.G. and C.B.F. changes were recorded continuously with a Sanborn Twin-Viso Cardiette.[4] The blood flow recording apparatus was calibrated so that 1°C. change in temperature produced an oscillation of 4 cm. on the recording paper. Electrocardiograms (Lead 11) were recorded simultaneously on a single channel Viso-Cardiette (Sanborn) in most cases. The direct (femoral) blood pressure changes were also recorded kymographically. All animals were heparinized (1 mg./kg.), and all drugs were injected in an exposed femoral vein. Chlorpromazine hydrochloride (Largactil) in powder form[5] was used, and solutions freshly made up as needed.

[4]The writers are indebted to Dr. John Feeney of St. Mary's Hospital, Montreal, for the loan of this instrument.

[5]Kindly supplied by Poulenc Ltd., Montreal.

Results

Figures 2 and 3 demonstrate some examples of the changes which were observed following repeated administrations of large doses of chlorpromazine (5 to 20 mg./kg.). Eight such experiments were performed.

As can be seen in Figure 2 at A and B following injection of 5 and 10 mg./kg. respectively, of chlorpromazine, there was a transient intense fall in blood pressure associated with some slight increase in heart rate. Concomitantly, the cerebral blood flow (C.B.F.) (nos. 2 and 3) showed a slight decrease, while there appeared to be relatively little change on the E.E.G. record. During the interval between the two recordings a further dose of 10 mg./kg. was given without much further change in the record, but a marked fall in blood pressure associated with an increase of the C.B.F. Following a third similar dose of the drug (C) the C.B.F. progressively increased as the fall in blood pressure persisted

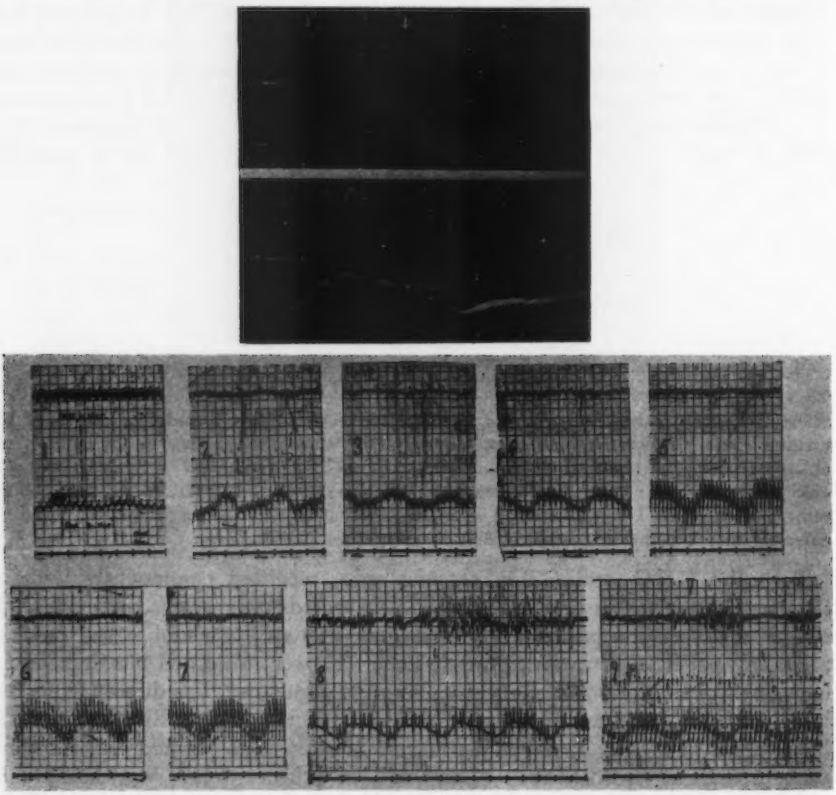


FIGURE 3. Dog, female, 8.6 kg. (*a*) The upper and lower kymographic records are continuations, and sections of (*b*) the associated E.E.G. (*above*) and E.C.G. (*below*) records, taken at nos. 1 to 9, as marked on the kymographic tracings, are shown. At A, B and C, respectively, chlorpromazine (10 mg./kg.) and at D, chlorpromazine (20 mg./kg.) were injected.

with no tendency to recovery. The electrical activity at this point also showed some increase in both rate and voltage (nos. 4 and 5).

Figure 3 shows again similar depressor responses following injections of chlorpromazine A, B, C and D, but the changes in electrical activity are more strikingly seen. Thus with the prolonged hypotension there is a progressive increase in heart rate, the E.E.G. showing at first a progressive slowing of electrical activity (nos. 2 and 3), followed by an increase in fast electrical activity (nos. 6 and 7), after the third dose of the drug (C), as compared to the pre-injection period (5). It is to be noted that when a larger dose (D) was given, periods of striking electrical outbursts developed (no. 8) and continued intermittently thereafter (no. 9).

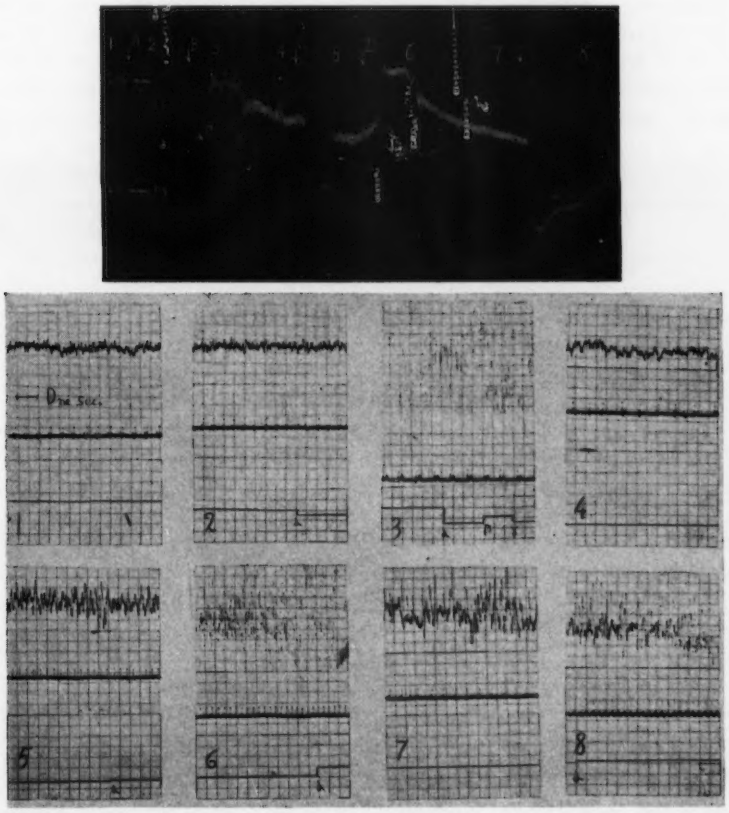
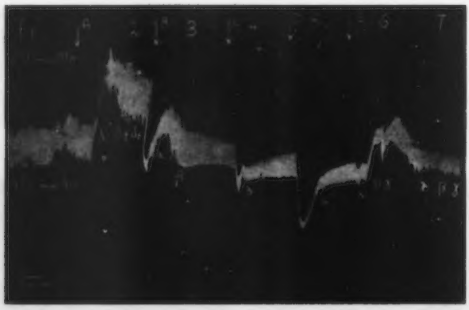


FIGURE 4. Dog, female, 7.4 kg. Kymographic record of blood pressure (*above*) and sections of associated E.E.G., E.C.G. and C.B.F. records (*below*) taken at nos. 1 to 8, as marked on the kymographic record, are shown. The changes in C.B.F. on nos. 2, 3, 6 and 8, marked α, β and γ correspond to those shown on the blood pressure record. At A and D, respectively, 10 mg./kg, and at B, 20 mg./kg. of metrazol were injected. At C, 10 mg./kg., and at E, 20 mg./kg., of chlorpromazine were given.

From the above findings it is evident that with prolonged and repeated administrations of high doses of chlorpromazine definite localized electrical outbursts can be observed under these conditions. On the other hand, as indicated in many of the initial responses, a single injection of the drug leads only to a decrease in cortical electrical activity.



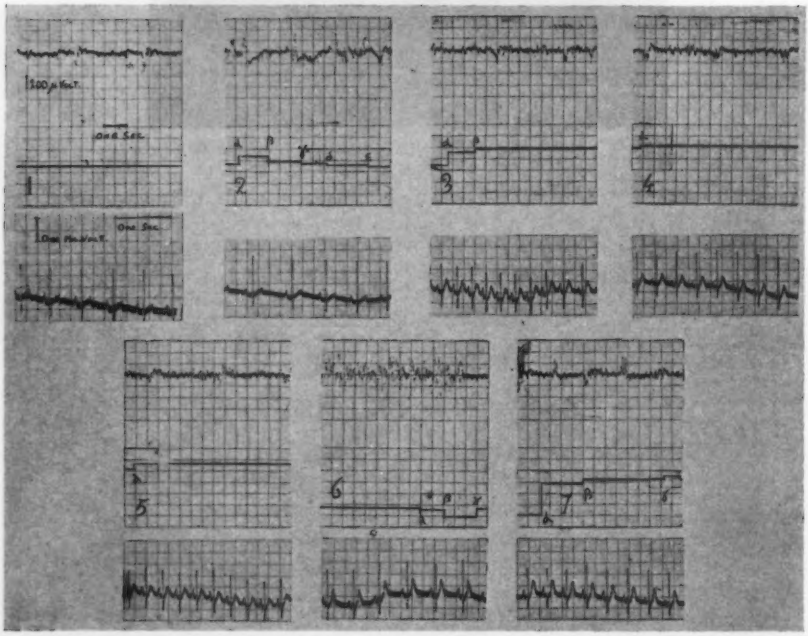


FIGURE 5. Dog, male, 12.0 kg. Morphinized (10 mg./kg.) before anaesthesia. Kymographic record of the blood pressure (*above*) and sections of associated E.E.G., C.B.F., and E.C.G. records (*below*) taken at Nos. 1 to 7, as marked on the kymographic tracing, are shown. On nos. 2, 3, 4, 5, 6, and 7 the changes correspond to the points marked by α, β and γ, on the record. Between nos. 5 and 6 the C.B.F. recording stylus had to be adjusted (lowered) in order to permit recording, and start of record no. 6 should therefore be considered as a direct continuation of the end of no. 5. At A and E, metrazol (10 mg./kg.), at B and D, chlorpromazine (10 mg./kg.) and at C, adrenalin (100 μgm.) were administered.

In the second series of experiments it was of interest to investigate the influences of chlorpromazine upon the responses to various central nervous system stimulants including metrazol, picrotoxin, nikethamide and methamphethamine. Some typical effects of the responses to metrazol are shown in Figures 4 and 5.

Following control injections of metrazol (A and B), one sees a rise in blood pressure associated with a marked outburst of cortical stimulation (no. 3). These effects were, however, accompanied by slowing of the heart and a considerable fall in the C.B.F. The pre-injection conditions were soon restored (no. 4), whereupon injection of chlorpromazine (C) rapidly induced marked tachycardia with increased E.E.G. activity and there was a slight increase in C.B.F. although there was a marked fall in blood pressure.

A subsequent injection (D) of metrazol (one-half of the dose previously employed at B) now induced a more intense and sustained rise in blood pressure and stimulation in E.E.G. activity. There was, however, no associated bradycardia and a rise rather than a fall in C.B.F. The excessive electrical activity persisted for the remainder of the experiment and appeared to be somewhat intensified (no. 8) by the injection of a further large dose of chlorpromazine (E). Indeed, the E.E.G. following chlorpromazine were now rather like those of metrazol, although the vascular changes were quite opposite. Similar results were observed in 8 other similar experiments.

Since it has been claimed that chlorpromazine can potentiate the central nervous system effects of analgesics, three similar experiments were performed on animals which were previously *morphinized*. A typical example of the findings is shown in Figure 5. As can be seen, under those conditions, the initial injection of metrazol (A) produces a good rise in blood pressure associated with moderate E.E.G. stimulation and a brief increase in C.B.F., which, however, returned to normal while the blood pressure was still maintained (no. 2). However, following chlorpromazine injection at B there was now only a *moderate* depressor response, associated with tachycardia, and a sustained increase in C.B.F., despite the fall in blood pressure (no. 3).

Somewhat similar changes were observed following an injection of adrenalin at C, as shown in record no. 4, and also following a repetition of the injection of chlorpromazine at D, as shown at no. 5. Finally, repetition of the metrazol injection at E, although still inducing a pressor response, associated with the usual marked cortical stimulation (nos. 6 and 7), there was an initial decrease followed by an increase in the rate of the C.B.F. It is therefore clear that *chlorpromazine enhances the cortical stimulating action of metrazol, both in the non-morphinized and morphinized animal under these conditions.* However, although metrazol increases blood pressure and reduces C.B.F., chlorpromazine leads to a fall in blood pressure and a marked increase in the C.B.F. It is also noteworthy that although chlorpromazine blocks the pressor response to injected adrenaline, the rise in blood pressure produced by metrazol still occurred. However, in other experiments in non-morphinized animals, following a large dose (20 mg./kg.) of chlorpromazine, the pressor response to metrazol was completely abolished although the cortical stimulation was still in evidence. The observed pressor response to metrazol is therefore an adrenergic effect.

Somewhat similar results were also obtained in similar experiments in which nikethamide (50 mg./kg.) was employed instead of metrazol. Under these conditions *the cortical stimulation following nikethamide is not abolished by chlorpromazine*, but the pressor response to the agent is reversed. No observations were made on the C.B.F. in this group of experiments.

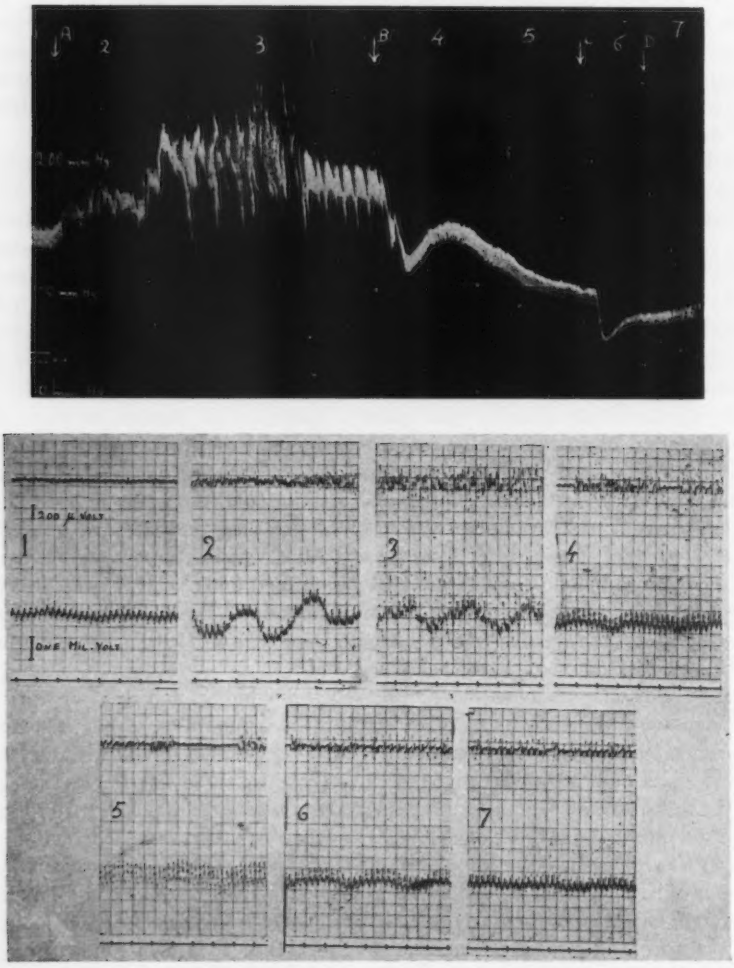
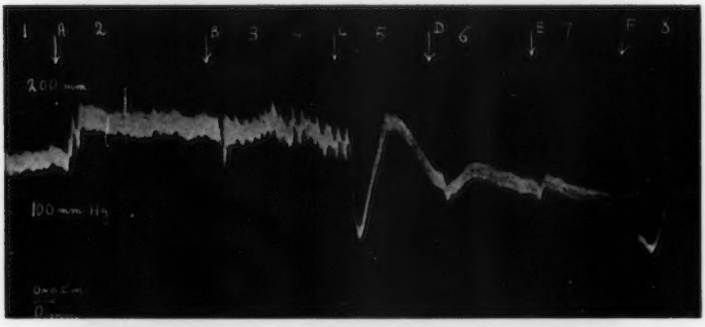


FIGURE 6. Dog, male, 9.5 kg. Kymographic record of blood pressure (*above*) and sections of associated E.E.G. and E.C.G. records (*below*), taken at nos. 1 to 7, as marked on the kymographic tracing, are shown. At A, picrotoxin (2 mg./kg.), at B and C, chlorpromazine (10 mg./kg.), and at D, picrotoxin (1 mg./kg.).

Figures 6 and 7 show typical examples of similar types of experiments in which the effects of chlorpromazine upon the responses to picrotoxin and methamphetamine were studied.



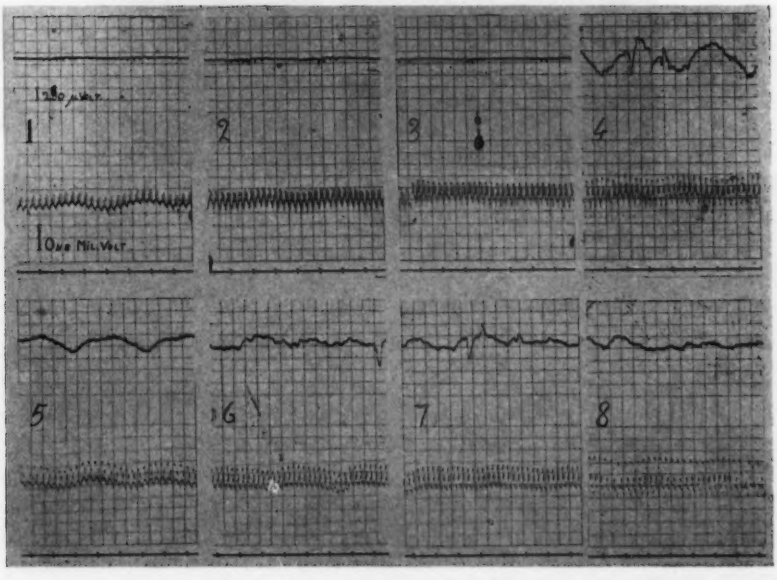
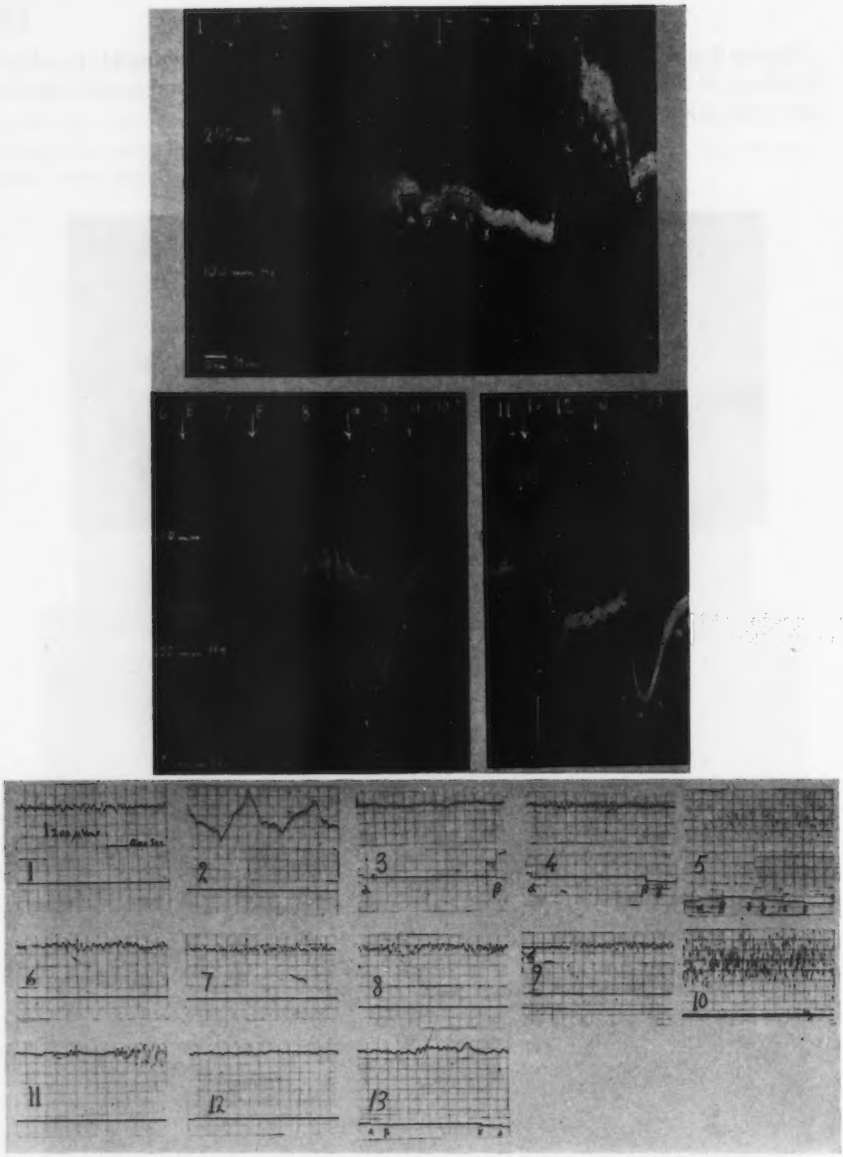
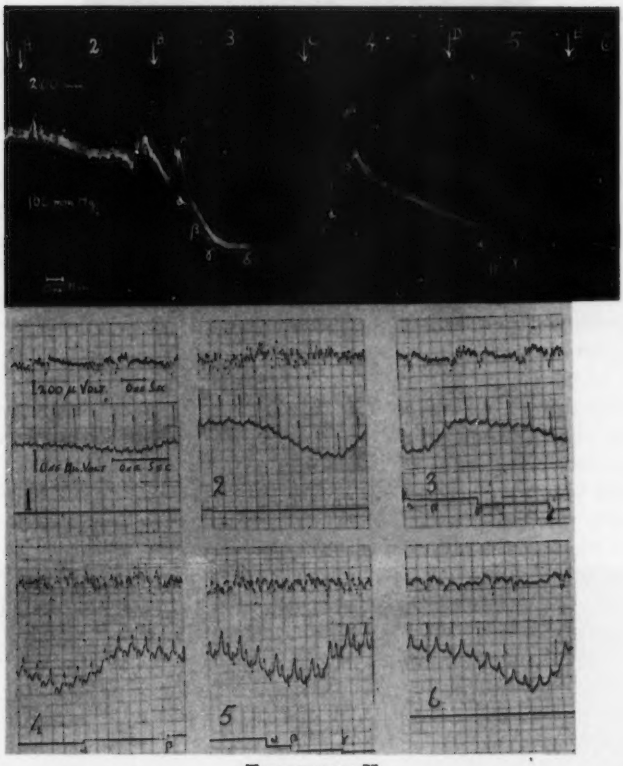


FIGURE 7. Dog, female, 14.2 kg. Kymographic records of blood pressure and sections of associated E.E.G. and E.C.G. records taken at nos. 1 to 8, as marked on the kymographic tracings, are shown. At A and B, methamphetamine (1 and 2 mg./kg., respectively), at C, chlorpromazine (10 mg./kg.), at D and E, metamphetamine (1 and 2 mg./kg., respectively), and at F, adrenalin (200 μgm.) were injected.



EXPERIMENT I

FIGURE 8. *Experiment I.* Dog, male, 9.4 kg. Kymographic record of blood pressure (*above*) and sections of associated E.E.C. and C.B.F. (*below*), taken at nos. 1 to 13, as shown on the kymographic records. On nos. 3, 4, 5 and 13 the changes correspond to the points marked by α, β, γ and σ. An interval of 18 minutes elapsed between the upper and the lower records and an interval of 16 minutes elapsed between the two lower sections. At A, D, E, and H, metrazol (10 mg./kg.), at B, C and F, ansolysen (0.7, 1.4 and 10 mg./kg., respectively), at C and J, chlorpromazine (10 mg./kg.) and at I, adrenalin (100 μgm.) were injected.

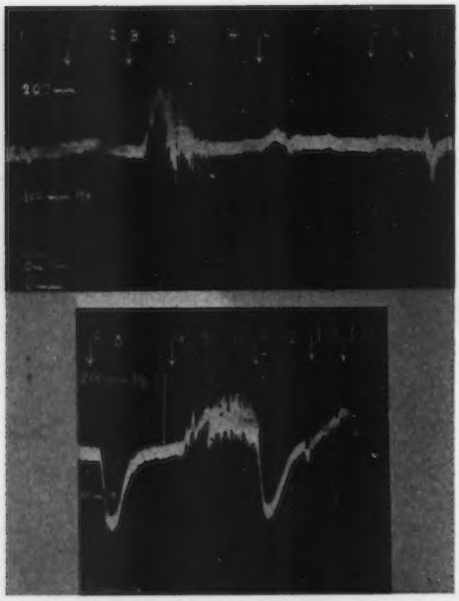


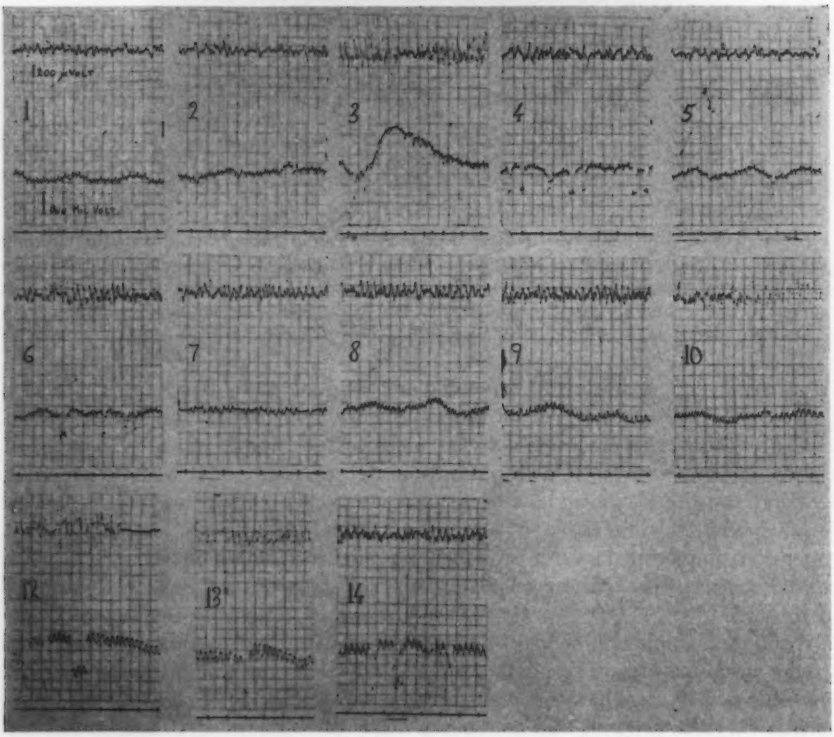
EXPERIMENT II

Experiment II. Dog, male, 8.2 kg. Record of blood pressure (*above*) and associated sections of E.E.G., E.C.G. and C.B.F. records (*below*), taken at nos. 1 to 6, as marked on the kymographic tracing, are shown. On nos. 3, 4, and 5 the changes correspond again to the points marked by α, β, γ, and σ. At A and C, metrazol (10 mg./kg), at B, hexamethonium (5 mg./kg.) at D, chlorpromazine (10 mg./kg.) and at E, adrenalin (200 μgm.) were injected.

As can be seen in Figure 6, following injection of picrotoxin (A), there is a progressive and sustained rise in blood pressure, associated with marked tachycardia and increased electrical activity of the cortex (nos. 2 and 3). Injections of chlorpromazine at B and C led to the usual depressor response with tachycardia, although the E.E.G. showed a curious alternation of high and low voltage waves (nos. 4 and 5), suggestive of excessive cortical stimulation and subsequent repetition of picrotoxin (D) produced no further changes in the E.E.G. The results suggest that *chlorpromazine does not prevent the cortical effects of picrotoxin.*

When methamphetamine was injected at A and B (Fig. 7), although there was a more sustained pressor response the E.E.G. showed only a slight initial stimulation followed by peculiar high voltage slow waves (no. 4). Following chlorpromazine (C) these waves still continued, although with reduced amplitude, but

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on repeated injection of methamphetamine (D and E) slow high voltage waves again reappeared. It is, therefore, clear that chlorpromazine *does not block the cortical effects of methamphetamine*. It is of interest to note that although picrotoxin and methamphetamine are central nervous system stimulants, their effect on electrical activity as recorded is quite different (compare Figs. 6 and 7).

Finally, some experiments were performed, in which chlorpromazine was injected following previous administration of (*a*) *ganglionic blockade*, induced either by injection of ansolyen or hexamethonium, or (*b*) *peripheral sympathetic blockade* induced by hydergin. Some examples of the results obtained are shown in Figures 8 and 9.

The most striking effects of the ganglionic blocking agents which were observed may be summarized as follows: (*a*) There was no significant change in the pressor or E.E.G. responses to metrazol (Fig. 8, upper and lower sections); and (*b*) There was no sustained depressor response or evidence of stimulated cortical electrical activity following *repeated* injections of chlorpromazine.

Following injection of the adrenergic blocking agent (hydergin) alone, both the E.E.G. outbursts and the pressor responses to injected metrazol were, however, abolished (Fig. 9, upper section), but subsequent *repeated* injections of chlorpromazine again led to neither the usual sustained depressor responses nor the increased cortical activity. Curiously enough, whep the responses to metrazol were tested after *both hydergin and chlorpromazine*, it is clear that both the usual E.E.G. outbursts and the pressor responses were restored. In addition, despite repeated chlorpromazine injections after hydergin the blood pressure was usually still well maintained and in some cases was higher at the end of the experiment than during the pre-injection control periods (see Fig. 9, lower section.) It would, therefore, appear that the hydergin-metrazol combination completely antagonizes the prolonged depressor effects of chlorpromazine, and associated with this action there was accentuation of the E.E.G. outbursts induced by chlorpromazine. This combination might, therefore, be of some antidotal value following excessive chlorpromazine administrations, and would appear to warrant further investigation in this connection.

Some Observations on the Effects of Diethazine (Diparcol)

Diethazine is a close chemical relative of chlorpromazine, and it was therefore of some interest to compare its effects with those of chlorpromazine under the conditions of these experiments.

In Figures 10 and 11 are illustrated some of the typical responses observed after repeated diethazine injections, and the influence of this agent upon the responses to metrazol. As is evident from Figure 10, the depressor responses to diethazine were much less sustained than those observed after chlorpromazine.

Figure 9. Dog, female, 7.5 kg. (*a*) The upper and lower kymographic records are continuous and associated sections of (*b*) the E.E.G. and E.C.G. taken at nos. 1 to 14, as marked on the kymographic tracings, are shown. At A, B, D, G and I, 5 mg., 15 mg., 10 mg., 20 mg., and 10 mg./kg., respectively, of metrazol were injected. Hydergin (0.3 mg./kg.) was given at C and J, and chlorpromazine (10 mg./kg.) at F and H.

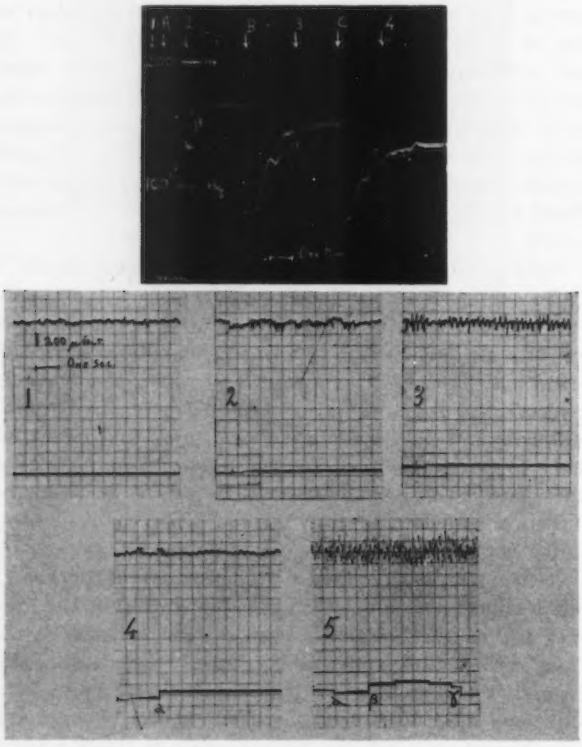

FIGURE 10. Dog, male, 17.0 kg. Kymographic record of blood pressure (*above*) and sections of associated E.E.G., and E.C.G. and C.B.F. (*below*), taken at nos. 1 to 4, as marked on the kymographic tracing, are shown. On No. 2 the changes recorded correspond to the points marked by α, β and γ. At A (5 mg.), and at B and C (10 mg./kg.) diethazine were injected.

These effects were also associated with more intense cortical stimulation and increased cerebral blood flow (nos. 3 and 4). In addition, both the central stimulation (E.E.G. outbursts) and the pressor responses following metrazol, appeared to be potentiated by diethazine, with concomitant augmented cerebral blood flow (Fig. 11). However, following sympathetic blockade with hydergin, all of these effects are antagonized. Thus, as can be seen from the records, both the usual pressor effect and cortical stimulation following metrazol are blocked. However, with superimposed diethazine in such experiments, these responses to metrazol are again restored.

It is also noteworthy that after injection of hydergin alone, the cerebral blood flow is decreased, despite the rise in blood pressure (Fig. 12, no. 4) and subsequent injections of metrazol or diethazine did not significantly restore the cerebral blood flow to normal although blood pressure again was well main-

tained. From the above findings, it is clear that the over-all effects of diethazine were rather similar to those of chlorpromazine, except that they were less sustained.

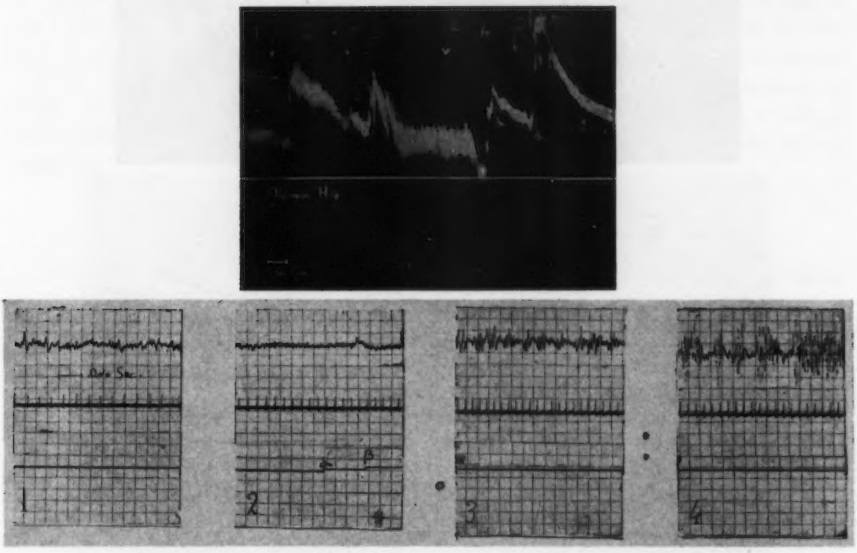

FIGURE 11. Dog, male, 9.6 kg. Kymographic record of blood pressure (*above*) and sections of associated E.E.G. and C.B.F. records (*below*), taken at nos. 1 to 5, as marked on the kymographic tracing, are shown. On nos. 4 and 5 the changes recorded correspond to the points marked by α, β and γ. At A, B and D, metrazol (10 mg./kg.), and at C, diethazine (5 mg./kg.) were injected.

SUMMARY AND CONCLUSIONS

In curarized dogs under artificial respiration, it was observed that (*a*) chlorpromazine in high and repeated doses (5 to 20 mg./kg.) can induce marked fall in blood pressure, tachycardia, and increased cerebral blood flow; (*b*) previous injections of similar high doses of chlorpromazine do not abolish either the pressor responses or cortical stimulation (outbursts) induced by metrazol, and both agents appear rather to lead to enhanced cortical outbursts; (*c*) chlorpromazine also does not affect the cortical stimulation (E.E.G. changes) following injections of nikethamide, picrotoxin, or amphetamine, *but antagonizes the blood pressure responses to these agents*; (*d*) after ganglionic-blockade (ansolysen or hexamethonium) cortical changes induced by chlorpromazine are not prevented, but its depressor response is lessened by ansolysen, but on the contrary enhanced by hexamethonium; (*e*) after sympathetic blockade (hydergin) both the central stimulation and pressor responses to metrazol are prevented, but the depressor response to chlorpromazine is antagonized and combined hydergin-metrazol treatment appears to prevent the usually observed depressor effects of

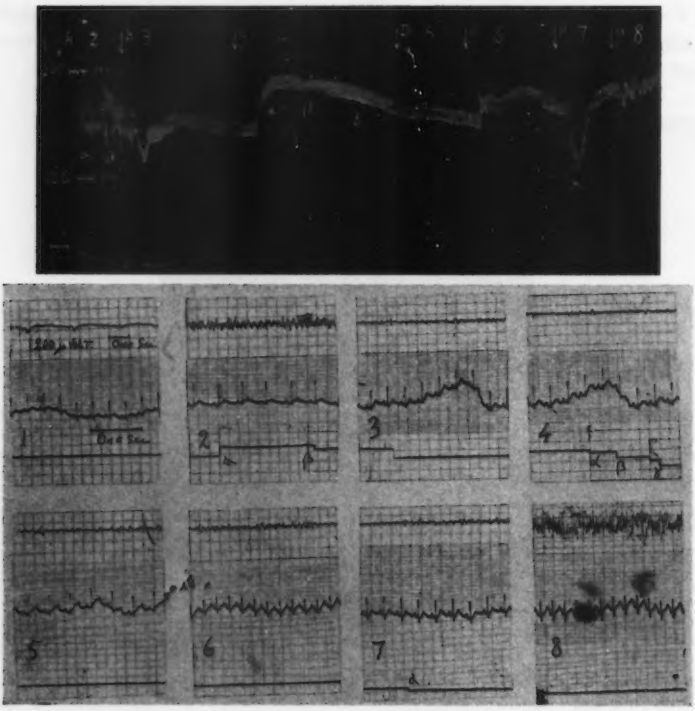

FIGURE 12. Dog, male, 7.4 kg. Kymographic record of blood pressure (*above*), and sections of associated E.E.G., E.C.G., and C.B.F. records (*below*), taken at nos. 1 to 8, as marked on the kymographic tracing, are shown. On nos. 2, 4 and 7 the changes recorded correspond to the points marked α, β and γ. At A, D, E and G, metrazol (10 mg./kg.) at B, diethazine (5 mg./kg.), at C, hydergin (1 mg./kg.) and at F, diethazine (5 mg./kg.) were injected.

excessive chlorpromazine injections; and (*f*) diethazine appears to exert similar actions to those of chlorpromazine, but its effects are less sustained.

RÉSUMÉ

Chez des chiens curarisés placés sous respiration artificielle, on a observé certaines réactions à savoir que (*a*) la chlorpromazine à hautes doses répétées (5 à 20 mg./kg.) peut produire une chute marquée de la pression sanguine, une tachycardie et une augmentation de l'afflux sanguin au niveau du cerveau; (*b*) les injections antérieures de telles doses elevées de chlorpromazine n'abolissent ni l'effect sur la pression ni la stimulation du cortex causés par le metrazol; les deux agents semblent plutôt produire des réactions électriques soudaines et violentes dans le cortex; (*c*) la chlorpromazine n'affecte pas la stimulation corticale, à la suite d'injections soit de coramine ou de picrotoxine ou de amphetamine, mais empêche les réponses de la pression sanguine à ces agents; (*d*) après un blocage

ganglionnaire (ansolysen ou hexamethonium) on ne prévient pas les changements corticaux apportés par la chlorpromazine, et l'effet depresseur est diminué par l'ansolysen alors qu'il est augmenté par l'hexamethonium; (*e*) après un blocage sympathique (hydergine) la stimulation centrale et l'effet sur la pression causés par le metrazol sont nuls. L'effet dépresseur de la chlorpromazine sur la circulation sanguine est inversé et le traitement à l'hydergine associé au metrazol semble prévenir cet effet dépresseur habituellement observé à la suite des injections de doses excessives de chlorpromazine; et qu'enfin, la diethazine semble produire les mêmes réactions que la chlorpromazine mais avec des effets qui sont moins soutenus.

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CARBON DIOXIDE ACCUMULATION: VALVE LEAKS AND INADEQUATE ABSORPTION[1,2]

JAMES H. KERR, M.B., and JOHN L. EVERS, PH.D.[3]

In the types of breathing circuits commonly used in general anaesthesia, valves are utilized to provide either unidirectional gas flow or a pressure release (pop-off). In the closed circle, satisfactory function is dependent upon the integrity of the valves; the occurrence of a defect allows reflux and an opportunity for re-breathing. In practice, two types of valve are in use to provide the unidirectional flow in the closed circle, the gravity-returned rigid disc and the rubber or plastic mushroom. The former type has been observed to become fixed in the open position during use; although more common at the expiratory valve, where condensation of water vapour from the patient's exhaled gases occurs, sticking has also been noted at the inspiratory side. The mushroom type of valve may become "fluted," wherein one segment of the valve protrudes through the supporting grid and is retained thereby; such an occurrence is usually the result of exposure to elevated back pressures as occurs when one forcibly breathes against a single valve.

It is primarily with the effect of leaks in these valves, expressed in terms of carbon dioxide rebreathed, that this presentation is concerned. However, as adequate carbon dioxide absorption is also of prime importance in the closed circle system, some observations are offered on the use of canisters, both in this and the to-and-fro system.

PROCEDURE AND EQUIPMENT

The procedure was designed to demonstrate the effect of valve leak or insufficient carbon dioxide absorption, at the same time taking into account the physiological response obtained from an unmedicated patient.

An Ohio 19-type circle and absorber was utilized for observations on its own built-in valves and other substituted valves in differing arrangements, with and without deliberately introduced leaks which simulated those which were observed in clinical practice. For the to-and-fro system, a standard Waters (8 x 13 cm.) canister was used.

The valves investigated were those built into the Ohio 19 canister and both the yoke and individually mounted valves produced by Anesthesia Associates, Inc.

Two Ohio 19 canisters were used; one contained fresh lime, the other had been used until it was allowing passage of 2 per cent carbon dioxide. Similarly, the Waters canisters contained fresh and used lime.

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[2]Presented at a meeting of the Ontario Division, Canadian Anaesthetists Society, Hamilton, Ontario, October 5, 1957.

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The analysing equipment consisted of a Liston Becker (Model 16) carbon dioxide analyser and a pneumotachograph. The dead space of this analysing equipment and mouthpiece was roughly that of a conventional mask, 110 cc. These two instruments, suitably calibrated, enabled us to obtain continuous measurement of flow rates and carbon dioxide concentrations of the respired gases. The signals from the carbon dioxide analyser and from the differential strain gauge attached to the pneumotachograph were amplified and recorded on Sanborn equipment. These two records, carbon dioxide concentration and flow, yield several parameters, including dead space.

Figure 1 illustrates the arrangement of mouthpiece, analysing equipment, and anaesthetic apparatus.

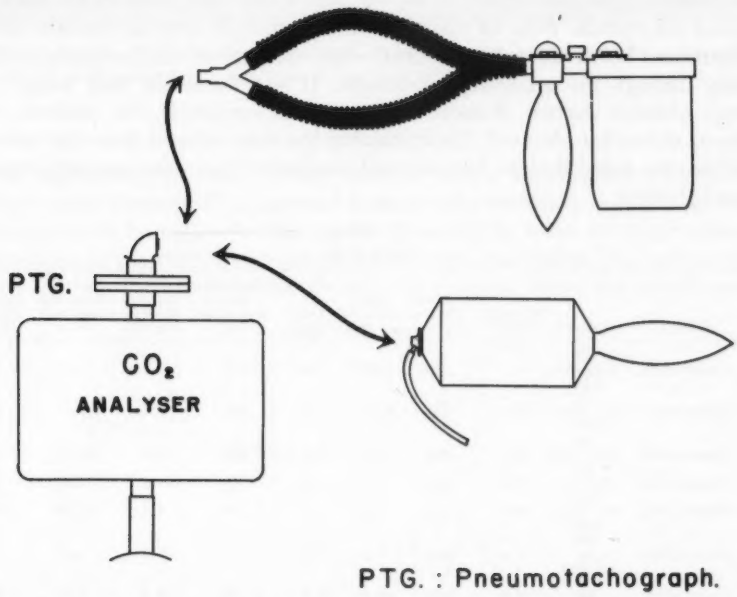

FIGURE 1. Illustrating the arrangement of mouthpiece, analysing equipment, and anaesthetic apparatus. The arrows indicate the position of attachment of the parts during the procedures.

The subject, unmedicated but under basal conditions, was first required to breathe through the analysing equipment until a steady state had been achieved. Thereafter, the various arrangements of anaesthetic apparatus were attached for short periods of time and their immediate effects recorded. Between procedures, a short period of air breathing was allowed during which the apparatus was thoroughly flushed and filled with carbon dioxide-free air. During observations on the closed circle and to-and-fro system, oxygen was added throughout at a rate of 250 cc. per minute. The subject had no knowledge of the particular changes that were being utilized and had been trained by previous experiments to allow his natural respiratory responses to occur without inhibition.

Results

The results given in Table I are obtained from single breaths at the time stated after the beginning of each procedure. These figures refer solely to the total volumes of gas and carbon dioxide content entering and leaving the anaesthetic apparatus; effects of instrumental dead space are excluded. Inspired carbon dioxide concentrations up to 6.3 per cent are recorded with a corresponding increase in tidal volume of almost 350 per cent. The conditions of the experiments would not allow the development of a steady state and in certain cases the changes were progressing rapidly towards carbon dioxide concentrations which would have caused considerable distress to our subject and denied the possibility of continuing with other observations. We noted also that some of the responses appeared anomalous. Four of our observations include alveolar carbon dioxide concentrations below the value obtained when the patient was breathing ambient air only through the analysing equipment. It will be noted that where such lowered alveolar carbon dioxide concentrations occurred, the patient's tidal volume is somewhat elevated. On examining the time interval from the previous procedure, we noted that we had allowed insufficient time for sustained response to have subsided.

TABLE I

Fresh Lime

Procedure	Circuit	Valves	Alveolar CO_2(%)	Tidal volume (cc.)	Rate (breaths per min.)	Time (min.)	Equivalent added dead space (cc.)	Average inspired CO_2 (%)	Total CO_2 inspired (cc.)	Minimum inspired CO_2 (%)
2	Closed circle	19 Exp. valve leak	6.1	725	10.5	1.25	170	1.4	10.5	3.4
3	Closed circle	19 Ins. valve leak	6.0	895	12.0	1.5	290	1.9	17.5	0.3
4	Closed circle	19 Both leak	6.7	955	9.5	1.5	830	5.9	56.0	3.8
5	Closed circle	AA Intact	5.3	825	7.0	1.75	10	<0.1	0.5	0.0
6	Closed circle	AA Ins. valve leak	6.1	735	8.5	1.25	185	1.5	11.0	0.0
18	Closed circle	SS At canister	4.4	1200	7.5	1.75	45	0.2	2.0	0.0
19	Closed circle	SS At patient	4.9	640	8.0	0.5	40	0.3	2.0	0.0
20	To and fro closed		5.6	790	7.5	1.0	40	0.3	2.2	0.0
Air			5.8	510	9.0	3.25	0	0	0	0.0

Valves: 19—gravity returned fibre disc type mounted on Ohio 19 canister
AA—Anesthesia Associates' valves mounted in yoke
SS—Anesthesia Associates' individually mounted valves (Sierra Silicone)

From the figures obtained, it is apparent that in closed circle, or to-and-fro systems, which are functioning correctly, there is only a slight elevation of inspired carbon dioxide. The introduction of the valvular leak in the circle system produces an immediate rise in the inspired carbon dioxide level. The additive effect of a double valve leak is demonstrated. The rapidity with which such levels can be attained can be seen from the reproductions of specimen recordings in Figure 2.

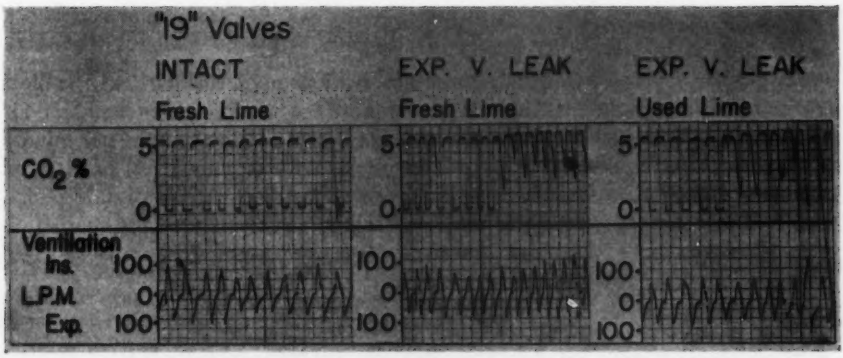

FIGURE 2. The rapid rise in the inspired carbon dioxide level immediately following the attachment of the anaesthetic apparatus is demonstrated.

DISCUSSION

The significance of these grossly elevated values for inspired carbon dioxide levels is most dramatically expressed in terms of ventilation required to maintain carbon dioxide homeostasis. The figures given in the table for tidal volume are expressions of the subject's efforts to achieve this goal under the various circumstances. In the absence of the steady state, they do not depict the actual increment

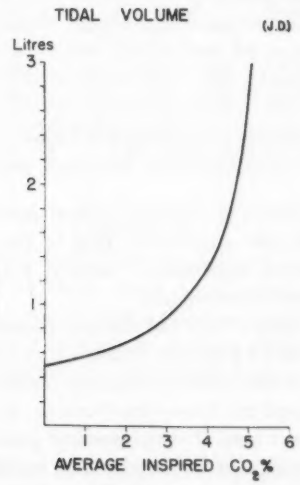

FIGURE 3

in ventilation necessary to compensate for a particular inspired carbon dioxide level. These relationships are expressed in the basic equation for pulmonary ventilation for a single breath at fixed frequency (1):

$$\text{tidal volume} - \text{dead space} = \text{alveolar ventilation} = \frac{CO_2 \text{ production}}{\text{alveolar } CO_2 \text{ fraction} - \text{inspired } CO_2 \text{ fraction}}$$

The graph (Figure 3) calculated from observations upon this particular subject (carbon dioxide production 192 cc. per minute) while breathing ambient air illustrates the alterations in his tidal volume at a rate of nine breaths per minute which would be required to achieve homeostasis with various levels of inspired carbon dioxide. To combat some of the levels of inspired carbon dioxide which were found in our procedures (Tables I and II), it can be seen that the ventilation

TABLE II
USED LIME

Procedure	Circuit	Valves	Alveolar CO_2 (%)	Tidal volume (cc.)	Rate (breaths per min.)	Time (min.)	Equivalent added dead space (cc.)	Average inspired CO_2 (%)	Total CO_2 inspired (cc.)	Minimum inspired CO_2 (%)
1	Closed circle	19 Intact	6.7	1280	6.5	3.5	335	1.8	22.5	1.5
2	Closed circle	19 Exp. valve leak	7.5	1310	7.5	3.5	855	4.9	64.5	4.4
3	Closed circle	19 Ins. valve leak	6.4	1235	7.5	7.5	685	3.6	44.5	1.2
4	Closed circle	19 Both leak	7.1	1730	8.0	5.5	1525	6.3	109.0	4.7
5	Closed circle	AA Intact	6.1	680	8.5	4.75	155	1.4	9.5	1.0
6	Closed circle	AA Ins. valve leak	6.1	915	7.0	4.25	390	2.6	24.0	0.5
7	Closed circle	AA Exp. valve leak	6.0	930	7.5	3.75	395	2.5	23.5	2.0
18	Closed circle	SS At Canister	5.3	1225	5.0	3.25	315	1.4	17.5	1.0
19	Closed circle	SS At patient	5.8	740	8.0	3.0	160	1.3	9.5	1.0
20	To-and-fro closed		5.8	705	10.0	5.25	120	1.0	7.0	0.5

VALVES: 19—gravity returned fibre disc type mounted on Ohio 19 canister
AA—Anesthesia Associates' valves mounted in yoke
SS—Anesthesia Associates' individually mounted valves (Sierra Silicone)

of a very high order is required to prevent carbon dioxide accumulation. As the inspired level of carbon dioxide approaches that of the subject's resting alveolar value, the required ventilation approaches infinity; with even higher values, no amount of effort would obtain homeostasis.

It will be noted that our subject did not manage to maintain his alveolar carbon dioxide at his resting level of 5.8 per cent during many of the procedures (2).

The results of including in the circuit a canister containing expended lime were as expected. The canister used for these observations, as already stated, had been correctly packed and utilized until it was allowing passage of 2 per cent carbon dioxide. At this point, the indicator in the granules on the surface had just begun to change colour which a casual glance would probably not have detected. We know from previous experiments that there is a considerable period between the onset of incomplete carbon dioxide absorption and the appearance of indicator change in the surface granules in this particular canister. Thus, to rely upon inspection of the surface lime is fallacious. Furthermore, there is no means of observing the lime indicator during use.

In the results obtained during the procedures when the Anesthesia Associates' valves were used instead of the valves on the canister, there are marked differences in the equivalent added dead spaces with the different valve positions. An equivalent added dead space of 10 cc. results with the yoke valves and fresh lime in the canister; it is increased to 40-45 cc. when the individually mounted valves are placed at either the patient or canister end of the corrugated tubes of the circle (Procedures 5, 18, 19). The values obtained for equivalent added dead space with used lime in the canister in the same procedures confirm the effects of the different placement of the valves.

Under normal clinical conditions for general anaesthesia, it is not always feasible to obtain continuous monitoring of respired carbon dioxide. Moreover, as drugs (3, 4) and surgical procedures modify the physical signs of carbon dioxide retention, its diagnosis becomes complicated and unreliable. This, in turn, signifies that the detection of elevated levels of inspired carbon dioxide is difficult. If the effect of the drugs and procedures of surgery upon the items in the equation for pulmonary ventilation are considered, the maintenance of carbon dioxide homeostasis is seen to be subject to many variables. Thus, increases in inspired carbon dioxide must be compensated by increases in ventilation commensurate with alterations in the other items concerned. It may be that the conditions of anaesthesia are such that a patient is capable of spontaneously maintaining a steady alveolar carbon dioxide concentration; more often this is not so, and it rests with the anaesthetist to augment the ventilation.

These studies demonstrate the fallacy of depending on even the most modern equipment and valves to provide reliable carbon dioxide elimination. That such levels of inspired carbon dioxide can occur, and be respired by subjects whose responses are obtunded, provides cause for some consideration.

It would seem opportune, at this point, to observe that where valvular defects occur and provide opportunity for rebreathing, the oxygen concentration will fall as the inspired carbon dioxide rises (5).

Comments

Although these observations have been performed with particular makes of equipment and valves, similar faults have been noted in other manufactured apparatus. The indictment of valves and soda lime containers is intended for all designs which respectively are subject to develop leaks or provide no simple means of determining adequate carbon dioxide absorption.

Summary

The effects on an unmedicated subject of valvular leaks and inadequate carbon dioxide absorption in a circle and a to-and-fro system are investigated. The results are expressed in terms of elevated percentages of inspired carbon dioxide, and the increase in ventilation required to maintain carbon dioxide homeostasis in a particular subject is calculated.

Attention is drawn to the dangers of high inspired carbon dioxide levels in general anaesthesia and the necessity for maintaining adequate ventilation.

ACKNOWLEDGMENTS

We are grateful to Doctors James O. Elam, Veronica Bakamjian, and Clinton D. Janney of this department for the advice and assistance so freely given in the preparation of the material for this paper.

RÉSUMÉ

Dans les circuits qu'on emploie courament en anesthésie générale, on place des valves, soit pour donner à l'atmosphère une seule direction, soit pour limiter sa pression. Dans le cas du circuit fermé, pour qu'il fonctionne de façon convenable, il faut que les valves soient étanches. Toute défectuosité entraîne un reflux et permet la respiration de l'air exhalé. Le premier but de ce travail est de montrer les conséquences des défectuosités de ces valves en ne considérant que la quantité de gaz carbonique réinspiré.

D'après les chiffres obtenus au cours de cette étude, il est manifeste que si les systèmes fonctionnent bien, qu'il s'agisse du circuit fermé ou du "va et vient," le taux d'élévation du gaz carbonique n'est que très faible. Si l'on provoque une défectuosité à une valve du circuit, le taux de gaz carbonique réinspiré s'élève immédiatement. Si la défectuosité est provoquée aux deux valves, les conséquences s'additionnent. La rapidité avec laquelle de hautes teneurs en gaz carbonique peuvent être atteintes est considérable ainsi qu'on peut le constater par les graphiques de la figure 2.

Dans l'occurrence de taux de gaz carbonique aussi élevés dans le circuit, le volume de ventilation nécessaire pour éviter l'augmentation du taux de gaz carbonique dans le sang devient effarant. Si l'on intercale dans le circuit un contenant de chaux efficace, les résultats sont éloquents comme le montrent les tableaux. Ces études démontrent l'imprudence sinon l'erreur de compter sur la machine, même la plus moderne, pour assurer l'élimination du gaz carbonique. Quand il survient des défectuosités aux valves, il s'ensuit une élévation du taux de gaz carbonique à cause de la réinspiration, et, si le taux de gaz carbonique augmente, le taux d'oxygène va diminuer.

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THE COMBINED ACTION OF PENTOBARBITAL AND MEPERIDINE, AND OF PROCAINE AND MEPERIDINE, IN GUINEA PIGS [1]

MADELAINE O. MAYKUT, PH.D.[2]

SEVERAL AUTHORS (1, 2, 3, 4, 5) have noted that meperidine reduces the amount of barbiturate required to produce adequate narcosis. It is known that morphine, to which meperidine is distantly related, prolongs the depressant action of barbiturates (6, 7, 8, 9). Recently a profound respiratory depression was reported with thiopental when premedication with morphine or meperidine was given (10). This respiratory depression had been reported earlier (11), but the degree of depression was not considered serious at the time since it was compared with that occurring with methadone.

On the other hand, reports have appeared (12,13) indicating that meperidine possesses local anaesthetic action preceded by preliminary irritation. It was therefore of interest to see whether meperidine would augment the action of procaine and whether the combined effect of meperidine and pentobarbital had both antagonistic and synergistic trends, as was previously found with procaine and pentobarbital (14).

MATERIALS AND METHODS

The substances used were Nembutal® (pentobarbital sodium), Demerol® (meperidine hydrochloride), and procaine hydrochloride (Novocaine®).

The experimental animals were white guinea pigs. Injections were made in areas where the hair was clipped and, when only one drug was injected, physiological saline replaced the injection of the second drug. The first of a series of experiments, during which each animal was closely observed, was designed to survey qualitatively the effects of the combination of two drugs. The most conspicuous and consistent symptoms were subsequently translated into symbols. From such a survey dosages of the two drugs could be chosen to give graded responses which could then be analysed.

The acute toxicities of the drugs, administered by intramuscular or subcutaneous injection, alone and in combination, were determined; all animals died within the 24-hour period. The LD50's (lethal dose) and their standard errors were estimated as described by Finney (15).

Pentobarbital and Meperidine

The average body weight of the guinea pigs was 624 gm. with a standard deviation of 144 gm.

Pentobarbital 2 per cent solution was injected in divided doses intramuscularly into the hind limbs of the animals, after which an injection of 4 per cent meperidine solution in divided doses was made intramuscularly into the fore limbs of

[1]The data included herein were taken partly from a Thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy, University of Toronto, May, 1957.

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the animals. Sleeping times indicated by the absence of the righting reflex were measured using ten animals at each dose level. The same animals were used only once a week since it had been reported (16, 17, 18, 19, 20, 21) that tolerance results in decreased sleeping time after the first few daily injections of pentobarbital.

Procaine and Meperidine

The guinea pigs used had an average body weight of 537 gm. with a standard deviation of 180 gm.

A 4 per cent solution of meperidine was injected in divided doses intramuscularly into the hind limbs of the animals following which 10 per cent procaine was injected subcutaneously on both sides of the back of the guinea pig.

Since convulsions produced by meperidine and procaine were intermittent and not continuous, it was decided that it would not be possible to use the duration of convulsive state as an index of action; instead it was decided to determine merely the CD50, that is, the dose required to produce convulsions. A total of 178 animals was used in these experiments, the number at each dose level ranging from 10 to 35 guinea pigs because the convulsive response obtained was irregular.

Results

Pentobarbital and Meperidine

Pentobarbital alone gave rise to sleep; meperidine alone produced convulsions.

The hypnotic action of the combined drugs was investigated, and the results are presented in Table I and in a three-dimensional diagram (Fig. 1a); this diagram is similar to that presented in a previous report on procaine and pentobarbital (14). The axes indicate concentrations of pentobarbital (N) and meperidine (D) expressed in logarithms, the height of the diagram representing the average duration of sleep in minutes. The lowest combination N_1D_1 represents 65 minutes and the highest N_3D_3 563 minutes. While the duration of sleep obtained with pentobarbital and meperidine increases with increasing concentrations of meperidine for all doses of pentobarbital, it should be noted that the concentration of meperidine must be increased considerably to bring about any change (Fig. 1a).

The data were subjected to statistical analysis using the logarithm of response. The χ^2 test for over-all homogeneity of variance, although slightly significant, did not vary significantly and the variance does not change with increasing doses

TABLE I

Duration of Sleeping Time in Minutes following Meperidine and Pentobarbital

Dose of Meperidine (mg./kg.)	Dose of pentobarbital (mg./kg.)		
	15	21.2	30
2	65.3	126.6	190.1
18	124.8	175.7	270.4
162	201.4	326.6	563.4

of either drug. It seemed reasonable, therefore, to calculate the results using the logarithm of the response since the data would be presented in a more straightforward fashion and the curved surface approaches a plane when the log response is used (Fig. 1b). The increase in sleeping time with increase in pentobarbital (N_1 to N_3) and meperidine (D_1 to D_3) is statistically significant. The slopes of the lines for increasing pentobarbital dose effects at each meperidine dose level are

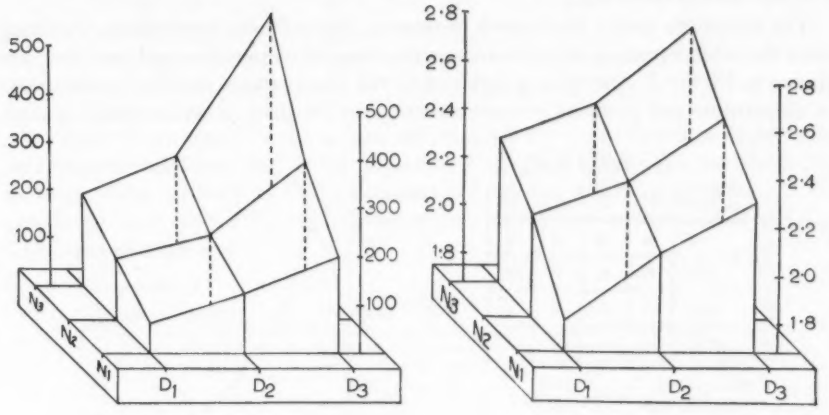

FIGURE 1. Hypnotic action of combinations of meperidine and pentobarbital in guinea pigs. The two horizontal axes represent increasing doses of the two drugs in logarithms; D stands for meperidine, N for pentobarbital: (*a*) the vertical axis represents sleeping time in min. (*b*) the vertical axis represents sleeping time in log min.

similar; the same is true for increasing meperidine dose effects at each pentobarbital dose level. Since the slopes are quite similar, interaction does not occur as is indicated in the analysis. On the basis of this statistical analysis the surface may be interpreted as a simple plane since no deviation from linearity occurs and the slopes are the same.

Table II lists the figures obtained for the acute toxicities of pentobarbital and meperidine, alone and in combination. The effect of meperidine on the LD50 of pentobarbital, as well as that of pentobarbital on the LD50 of meperidine is

TABLE II

ACUTE TOXICITIES OF PENTOBARBITAL AND MEPERIDINE(INTRAMUSCULAR) ALONE AND IN COMBINATION

	LD50 mg./kg.	±S.E.	Slope*	Number of guinea pigs
Pentobarbital	70.3	±4.7	7.9	35
Pentobarbital +35 mg./kg. meperidine	46.5	± 6.5	7.1	40
Meperidine	111.0	±14.0	9.2	30
Meperidine ±10 mg./kg. pentobarbital	315.0	±22.0	14.6	40

*Probit units per log dose.

significant. In the presence of meperidine (35 mg./kg. which is less than LD1) the LD50 of pentabarbital is decreased to 46.5 mg./kg. This amount of pentobarbital when used alone is equivalent to LD4. The toxicity of meperidene is decreased by pentobarbital, the LD50 being raised from 111 mg./kg. to 315 mg./kg. The latter amount of meperidine alone is equivalent to LD92.

Procaine and Meperidine

The symptoms noted, excitement, tenseness, unsteadiness, convulsions, resulting from the administration of various concentrations of meperidine and procaine, are shown in Figure 2. Attention is directed to the observations that the combination of meperidine and procaine is more toxic than either drug alone in similar dosage.

DEMEROL

PROCAINE mgm. per kgm.	2.5	5	10	20
0	N	N	N	E
100	N	E	T	T+E
200	G	X	X	X
400	X	X	X	X

N = normal T = tense

E = excited G = groggy

X = convulsions

FIGURE 2. Symptoms of individual guinea pigs given various dose combinations of meperidine (Demerol) and procaine.

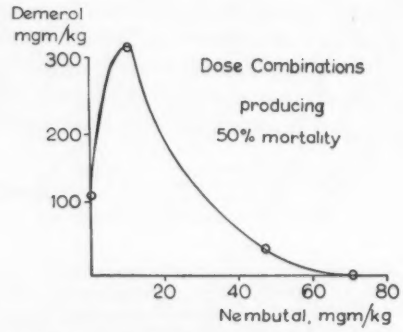

FIGURE 3. Lethal action of meperidine (Demerol) and pentobarbital (Nembutal), alone and in combination, in guinea pigs.

The values obtained for the CD50 of meperidine and of procaine are shown in Table III. When one-half the CD50 of both drugs was injected, the combined effect resembled potentiation; it was expected that 41.5 mg./kg. meperidine and 90.5 mg./kg. procaine injected into 40 animals would give a 50 per cent response but an 87.5 per cent response was observed.

The results obtained by combining procaine and meperidine in various doses are indicated in Table IV. This table shows that an increase in percentage of convulsions occurs with increasing procaine doses at all meperidine dose levels and a similar increase occurs with increasing meperidine doses at all procaine levels, but an erratic trend can be noted at the 9.0 mg./kg. meperidine level.

TABLE III

CONVULSIVE DOSE 50 OF MEPERIDINE AND PROCAINE ALONE

	CD50 (mg./kg.)	±S.E.	Slope	Number of guinea pigs
Meperidine (intramuscular)	83.1	±9.9	12.6	35
Procaine (subcutaneous)	180.9	±28.0	6.8	40

TABLE IV

PERCENTAGE OF CONVULSIONS IN GUINEA PIGS FOLLOWING MEPERIDINE AND PROCAINE

Dose of procaine (mg./kg.)	Dose of meperidine (mg./kg.)			
	4.5	6.5	9.0	12.5
104	20	40	36	40
125	35	50	50	72
150	70	80	61	100
CD50	134.5	119.0	126.6	110.1
±S.E.	17.5	17.9	21.5	8.8

In Table V are recorded the values obtained for the acute toxicities of procaine and meperidine, alone and in combination. The effect of procaine on the LD50 of meperidine, as well as that of meperidine on the LD50 of procaine, is not significant; meperidine 90 mg./kg. represents LD42 and procaine 402 mg./kg., LD45.

TABLE V

ACUTE TOXICITIES OF MEPERIDINE AND PROCAINE ALONE AND IN COMBINATION

	LD50 (mg./kg.)	±S.E.	Slope*	Number of guinea pigs
Meperidine†	111	±14	9.2	30
Meperidine +300 mg./kg. procaine	90	±5	11.7	30
Procaine†	438	±23	10.4	30
Procaine ±35 mg./kg. meperidine	402	±76	5.4	40

*Probit units per log dose.
†Meperidine given intramuscularly, procaine subcutaneously.

DISCUSSION

Pentobarbital and Meperidine

The results obtained are similar to those previously reported for pentobarbital and procaine (14). That is, meperidine like procaine, increases the toxicity of pentobarbital. Further, pentobarbital appears to antagonize the effects of meperidine since the LD50 of meperidine is raised in the presence of pentobarbital. These double effects are represented graphically in Figure 3. In such a plot a strictly additive effect of the two drugs would be characterized by points lying on a straight line joining the LD50 of meperidine and the LD50 of pentobarbital (22). The hump in the curve represents the antagonistic effect of pentobarbital and meperidine; the lower part of the curve indicates that the central depressant action of meperidine is very nearly additive to that of pentobarbital. From this it could be argued that a patient under the toxic influence of meperidine might be saved by the administration of pentobarbital, whereas in a case of barbiturate poisoning an additional injection of meperidine might prove fatal. Furthermore, these investigations emphasize that meperidine has two independent actions on the central nervous system; one is the production of convulsions, and this effect

is counteracted by pentobarbital; the second action is a depressant one and augments the action of pentobarbital. Isonicotinic acid hydrazide (INA) and some related compounds appear to have similar actions to procaine and meperidine when combined with pentobarbital (23). That is, pentobarbital action is prolonged by these compounds, and it antagonizes the stimulant action of INA on the central nervous system. Other drugs which have been reported to enhance the action of barbiturates are benadryl (24), thiambutene (25), 5-hydroxy tryptamine (26, 27), sulfonamides and derivatives (28, 29, 30), disulfiram (31), antihistamine (32), chlorpromazine (33), SKF 525A (34, 35), reserpine (36), and serotonin (37).

Acute toxicity studies of meperidine have been conducted in many species such as the mouse, rat, rabbit, cat, and dog, using various routes of administration (38). The present data cannot be compared since results were obtained on guinea pigs using the intramuscular route. However, the symptoms of excitement and convulsions observed were similar (39).

Procaine and Meperidine

The toxicities for both drugs, procaine and meperidine, were increased by using them in combination, as may be seen from the graphical presentation of the results (Figs. 4 and 5). The contours of the curves indicate that the convulsive effects of the two drugs combined are more than additive, whereas the lethal effects of the drugs are less than additive.

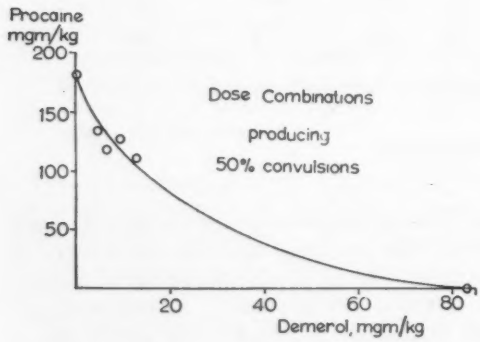

FIGURE 4. Convulsive action of meperidine (Demerol) and procaine, alone and in combination, in guinea pigs.

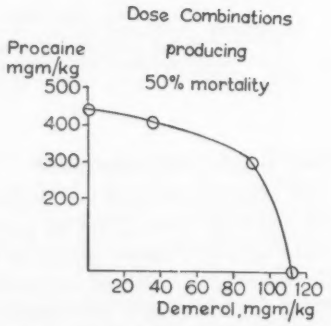

FIGURE 5. Lethal action of meperidine (Demerol) and procaine, alone and in combination, in guinea pigs.

Both drugs, meperidine and procaine, produce convulsions but the mechanisms responsible for this action may be different, since the slopes obtained for the CD50 of the drugs are different (Table III). However, the drugs combined produce additive effects. Also the slopes obtained for the CD50 (Table III) and the LD50 (Table V) of procaine as well as of meperidine are different, which may indicate that the mechanism of action giving rise to convulsions differs from that

causing death. Similar potentiation phenomena hve been reported (40) where the analgesic effect of some drugs increases with the simultaneous administration of local anaesthetics and a synergism of acute toxicity occurs when quinidine, meperidine, and procaine are used in combination (41).

Summary

Meperidine increases the sleeping time induced by pentobarbital in guinea pigs.

The effect of pentobarbital on the toxicity of meperidine was antagonistic, whereas the effect of meperidine on the toxicity of pentobarbital was nearly additive.

The results of these experiments show that pentobarbital will protect experimental animals against the convulsive effects of meperidine and that the depressant action of pentobarbital is augmented by the presence of meperidine. It has been pointed out that when meperidine and procaine are combined there is a potentiation of convulsive effects, but their combined lethal effects, while greater than that of either one alone, are not additive.

Acknowledgments

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Résumé

Des résultats expérimentaux ont laissé croire que la meperidine (Demerol®) avait un certain pouvoir comme anesthésique local et qu'elle pourrait diminuer également la quantité de barbiturique requise pour produire une narcose satisfaisante. Il nous a donc paru intéressant de vérifier si la meperidine n'augmenterait pas l'action de la procaine (un anesthésique local) et de vérifier également si l'effet associé de la meperidine et du pentobarbital (un barbiturique) ne présenterait pas des tendances à la fois antagoniste et synergique comme on l'avait découvert au préalable pour la procaïne et le pentobarbital.

Chez les cobayes, l'expérience a démontré que la meperidine augmente la durée du sommeil provoqué par le pentobarbital. Nous avons déterminé les doses toxiques (LD50) de ces médicaments employés seuls ou associés. Sur la toxicité de la meperidine, la pentobarbital s'est révélé un antagoniste et, sur la toxicité du pentobarbital, la meperidine a semblé avoir un effet presqu 'additionnel. Les résultats de l'expérience font croire que le pentobarbital peut protéger les animaux contre les effets convulsivants de la meperidine et que cette même meperidine augmente l'action déprimante du pentobarbital.

Si l'on associe la meperidine et la procaïne, il se produit une potentialisation de leurs effets convulsivants mais leurs doses léthales associées ne s'additionnent pas bien qu'elles soient plus grandes que l'une ou l'autre seule. Les mécanismes en jeu à l'occasion de convulsions peuvent être différents puisque les courbes obtenues pour les doses convulsivantes de ces médicaments 50 (CD50) sont différentes. Ainsi, les courbes obtenues pour le CD50 et le LD50 de l'un ou l'autre des médicaments, sont différentes, ce qui peut laisser croire que le mécanisme qui entre en jeu à l'occasion de convulsions est différent de celui qui cause la mort.

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ADRENERGIC BLOCKING AGENTS IN SHOCK[1]

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IN RECENT YEARS a number of agents have been developed which block the sympathetic nervous system. These agents can be divided into two groups according to their site of action: ganglionic blocking agents block the transmission of impulses at the ganglionic synapses; adrenergic blocking agents act on the sympathetic end organs and reduce or reverse the pressor effect of adrenalin. The latter group includes agents like dibenamine, dibenzyline, regitine, priscoline, hydergine, and chlorpromazine (Largactil).

Especially for chlorpromazine and more recently for hydergine, claims have been made that these agents would prevent shock caused by haemorrhage and severe trauma or would at least delay the onset of an irreversible state of shock. Laborit's (15) concept of artificial hibernation, in which Largactil plays the principle role, has received wide publicity, particularly in regard to its application in shock. Clinically, adrenergic or ganglionic blocking agents have been advocated for protection against shock and, in addition to blood volume replacement, for the treatment of existing shock (3, 7, 17). The reports of such treatments appear to be noteworthy and one has the impression that adrenergic blocking agents in combination with blood volume replacement would give better results than the present treatment of shock with transfusions and supportive measures. The value of many of the publications, particularly those from Europe, is discounted because they are written in a flowery language with specially invented terminology, and because the argumentation is frequently based on very theoretical grounds.

The basic concept for this new approach appears to be this. A diminished blood volume leads to a decrease in venous return and a reduced cardiac output. The resulting fall in blood pressure is counteracted by peripheral vasoconstriction, which is induced and possibly maintained by the activity of the sympathetic nervous system including the adrenal medula. This vasoconstriction in reducing the blood flow produces tissue hypoxia, which leads to an increased capillary permeability. Leakage from the capillaries reduces the blood volume further and thus a vicious cycle is set into operation (Fig. 1).

The important concept in this "shockwheel" is that compensatory mechanisms contribute to the progress of shock. Erlanger and Gasser (6) in 1919 expressed the view that the increased adrenergic activity in shock was an important factor in the deterioration of the organism. It was later on demonstrated that a continuous infusion of adrenalin could produce shock (8), and a marked rise of the blood level of adrenalin was observed following haemorrhage in dogs (23).

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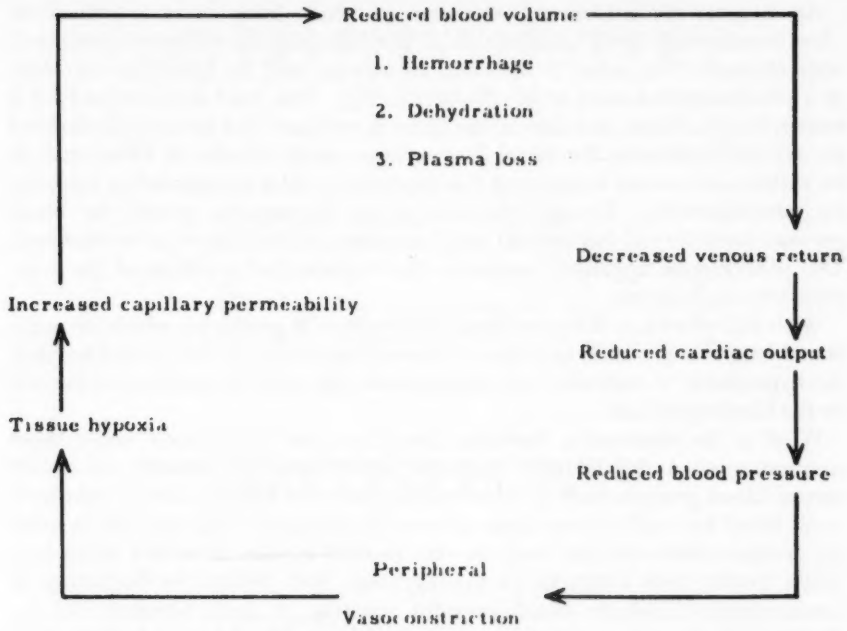

FIGURE 1. Shock wheel (21).

If such an overactivity of the sympathetic system is important for the production of an irreversible state of shock, then the pharmacological inhibition of this system should prove beneficial. Experiments on haemorrhagic shock in dogs and rats seemed to demonstrate this. It was shown in a number of studies (2, 12, 16, 18–20, 24) that the survival rate following a haemorrhagic shock procedure was markedly increased if an agent with an adrenergic blocking effect had been given before or shortly after the haemorrhage. It appeared as if adrenergic blocking agents offered a form of protection against irreversible shock.

Attempts have been made to use these findings as the basis for a new approach to the prevention and treatment of clinical shock (3, 17). The results of such a treatment are difficult to judge since no reliable signs exist to determine objectively the severity of a state of shock. Enthusiastic reports have been published in Europe. Laborit's cocktail was tried by the French Army in Indochina, but reports (5) failed to provide convincing results. However, there seemed to be difficulties in the practical handling of this new method. In an attempt to compare the new approach with the "classical" method on patients, Benke (1) concluded that the results with chlorpromazine and hydergine were not convincingly better.

In view of these reports the question is whether we should consider the sympathetic system as potentially dangerous and block it whenever the organism is threatened by severe stress or whether we may still have some sympathy with it?

An analysis of experimental haemorrhagic shock leads to some difficulties. Most investigators use a modification of the following procedure to produce a state of shock. The animal is bled into a reservoir until the blood pressure falls to a pre-determined mean level (35–45 mm. Hg). This level is maintained for a certain length of time, and then all the blood is reinfused and the animal observed for survival. Following the initial haemorrhage, small volumes of blood have to be withdrawn in order to maintain the hypotension. This is regarded as evidence for vasoconstriction. Towards the end of the hypotensive period the blood pressure tends to fall further and small amounts of blood have to be reinfused. This phenomenon apparently expresses the beginning of a failure of the compensatory mechanisms.

With this procedure a hypovolemic hypotension is produced, which, if maintained long enough, leads to a state of irreversible shock. In this procedure, only the hypotension is controlled; the hypovolemia can only be measured indirectly by the bleeding volume.

What is the relationship between blood loss and hypotension under these circumstances? A dog in light Nembutal anaesthesia will maintain an almost normal blood pressure until a considerable volume of blood is lost; a relatively small blood loss will then produce a severe hypotension. Yet, attempts to raise the pressure above this low level are very marked in spite of further blood loss. When treated with Largactil (2 mg./kg.) one hour before the beginning of haemorrhage, a definite blood pressure response to each bleeding can be observed, the low pressure level is reached with less blood loss and attempts to raise the blood pressure are less marked (Fig. 2).

This demonstrates the fact, well known to anaesthetists, that the difference between a normal and a "shock-level" of blood pressure corresponds to a relatively small change in blood volume. Inhibition of sympathetic activity produced this shock level of blood pressure with a smaller loss of blood. It might then be postulated that the blood loss which caused a severe hypotension in a treated animal may not be sufficient to produce a dangerous hypotension in an untreated animal. Blood volume studies have indicated that there seems to be a critical degree of hypovolemia which determines the reversibility of a state of shock following haemorrhage (22). Surgically sympathectomized dogs could tolerate severe hypotension longer, but their tolerance to blood loss was diminished (9). Most experimental studies on haemorrhagic shock showed that the bleeding volumes of animals treated before the haemorrhage with blocking agents were smaller than in the untreated controls. Even where the bleeding volumes were equal, the time necessary to withdraw the blood was considerably longer in the treated animals, if a comparable degree of hypotension was maintained (18). Thus, if hypovolemia is regarded as the principal factor in the production of a state of shock, it becomes doubtful whether the treated animals have been subjected to a comparable degree of stress in this type of experiment. Jacob *et al.* (14) state that the protective effect of dibenamine is mainly due to this reduction of the bleeding volume.

If this difference in bleeding volumes between treated animals and controls represents an important factor, then treatment with these agents should be only

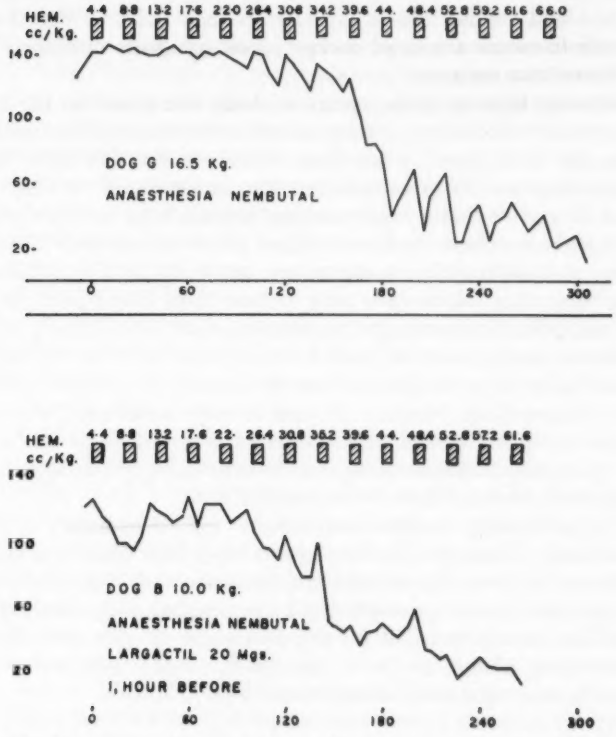

FIGURE 2. Blood pressure response to haemorrhage (mean pressure). Each column above tracing represents a blood loss of 4.4 cc./kg. Blood pressure in mm. Hg, time in minutes.

of value as long as the bleeding volume can be reduced during the experiment, that is, for a short period following the initial haemorrhage. At the University of Western Ontario studies were carried out to determine the value of adrenergic blocking agents for the treatment of shock. Lotz *et al.* (16) found that dibenamine and dibenzylene increased the survival when given 30 minutes after the initial haemorrhage. Since the dogs were connected to an open reservoir, the injection of the drug was followed by an uptake of blood into the animal and therefore the total bleeding volumes were less than in the controls. Treatment given 85 minutes after the haemorrhage was without benefit. Priscoline in dogs (10) and chlorpromazine in rats (4) did not increase the survival rate if these agents were given shortly before or together with the reinfusion of the withdrawn blood. Chlorpromazine in dogs, when given at the time of reinfusion, seemed to shorten the time of survival (11). Gowdey *et al.* (10) conclude that the beneficial effect of adrenergic blocking agents is largely dependent upon an increase in blood volume concomitant with the vasodilatation, and that it could be predicted that in the treatment of clinical haemorrhagic shock these agents

would be without value or even prejudice survival without a simultaneous replacement of blood volume. These experiments then failed to demonstrate that treatment with transfusion and adrenergic blocking agents combined would be superior to transfusion treatment alone.

The use of adrenergic blocking agents in shock was based on the assumption that an overactivity of the sympathetic system is detrimental in a state of hypovolemia. On the other hand, it has been demonstrated that these same compensatory mechanisms are essential for the maintenance of life in severe hypovolemia. Dogs survived a single massive haemorrhage of 4 per cent of their body weight without volume replacement, but pre-treatment with 2 or 5 mg./kg. of chlorpromazine made such a haemorrhage uniformly fatal (13). Furthermore, it was found that dogs which were able to raise their blood pressure following a period of controlled haemorrhagic hypotension, that is, to produce a prolonged and more intense vasoconstriction, had a better prognosis (10). Larger bleeding volumes have been reported for survivors in contrast to fatalities in studies of experimental haemorrhagic shock (12), and it may be assumed that this could be in part due to a more intense vasoconstriction. These findings cast some doubt on the concept vasoconstriction in response to hypovolemia is an important factor for the progression of shock into an irreversible state.

It is felt that differently designed experiments will be necessary to clarify this problem. Certainly adrenergic blocking agents have their place and their indications and the use of drugs like chlorpromazine may be desirable in certain conditions. On the basis of the presently available experimental evidence, however, these agents should only be used for the prevention of operative shock with a good understanding of the circulatory aspects involved. Their use in the treatment of already existing shock does not seem to be justifiable.

Summary

Premedication with adrenergic blocking agents in experimental haemorrhagic shock pocedure increases the tolerance to hypotension but diminishes the tolerance to hypovolemia. The experimentally observed protection against irreversible shock by such agents appears to be mainly due to a reduced blood loss, which is technically unavoidable in the experimental procedures usually employed.

There is no experimental evidence that adrenergic blocking agents are of value in the treatment of shock at a time when transfusion therapy fails. There is also no indication that a combination of blocking agents and volume replacement would be superior to blood volume replacement alone.

Résumé

Au cours des dernières années, on a préconisé, pour la prévention ou le traitement du choc causé par un traumatisme grave ou une hémorragie, l'association des agents ganglioplégiques et adrénergolytiques comme l'Hydergine et le Largactil avec la restitution du volume sanguin. La justification d'un tel traite-

ment semble découler du principe que la vasoconstriction consécutive à une réduction de volume sanguin, vasoconstriction attribuable à une activité sympathico-surrénalienne accrue, déclancherait un cercle vicieux qui conduit à un choc irréversible. Ainsi, l'inhibition du sympathique s'avérevait profitable.

Des résultats cliniques nous ont donné l'impression que l'association de l'emploi des agents adrénergolytiques en même temps que la restitution du volume sanguin constituerait un meilleur traitement dans le choc. Il est difficile de juger ces cas, car on ne peut pas déterminer objectivement la gravité d'un état de choc clinique.

Chez les animaux en choc hémorragique expérimental, le taux de survivance a semblé supérieur quand on faisait usage avant ou immédiatement après l'hémorragie des agents adrénergolytiques. Au cours de ces expériences, on provoque une hypotension prononcée en faisant une saignée dans un réservoir et, à un moment fixé au préalable, on injecte de nouveau le sang soutiré dans la circulation. On a observé, toutefois, chez les animaux traités que, pour maintenir cette hypotension, il fallait retirer des volumes de sang moins considérables. On a pu démontrer, chez les chiens, qu'une dose de Largactil de 2 mg./kg. administrée avant une hémorragie lente, entraînait une hypotension plus prononcée avec une perte de sang moindre et diminuait la tendance de l'organisme à élever la tension artérielle. D'où l'on présume que, à un degré comparable d'hypotension, les animaux traités garderaient un plus grand volume sanguin que les animaux non traités ou, encore, que l'hypotension, chez les animaux non traités, serait moins prononcée à saignée égale. En conséquence, le taux de survivance plus élevé, chez les animaux en hypotension provoquée par une hémorragie et traités au préalable avec des agents adrénergolytiques, semble être attribuable principalement à une perte sanguine inférieure.

Dans les cas où l'on a pratiqué des saignées d'un volume égal et où l'on a administré des agents adrénergolytiques tardivement au cours de l'hypotension confirmée ou encore en même temps que l'injection du sang soutiré, on n'a pas trouvé de différence dans la durée de survie ou cette durée était plus courte. En somme, après ces expériences, on ne peut pas affirmer que l'association de la restitution du volume sanguin et de l'usage des agents adrénergolytiques soit supérieure à la restitution du volume sanguin seule.

Nous avons l'impression que l'usage des agents adrénergolytiques devrait être limité à la prévention du choc opératoire et seulement si l'on a une parfaite compréhension des problèmes circulatoires en cause et que cet usage, dans le cas de choc confirmé, ne semble pas justifiable.

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EFFICACY OF ATARACTIC DRUGS IN CLINICAL ANAESTHESIA: A REVIEW

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COOLNESS and presence of mind under all circumstances, calmness amid storm, clearness of judgment in moments of grave peril, immobility and impassiveness are all synonymous with imperturbability or equanimity. These qualities were of the highest order to be attained by physicians in the opinion of Sir William Osler (1). In the three generations since Osler uttered his sermon on Aequanimitas, physicians have been trying to transfer these qualities to their patients because they know that mental stress and chronic anxiety aggravate physical debility and disease states.

For many years the clinician has employed such drugs as alcohol, barbiturates and other types of hypnotics, bromides, paraldehyde, and a variety of analgesic-sedatives, to calm the anxious patient. Success with these agents has been variable. Morphine is still the first choice for the relief of traumatic pain. Salicylate derivatives provide excellent relief from inflammatory and congestive pain and the associated mental anguish. Caffeine and amphetamine and their derivatives are still favourites for the relief of mental depression and fatigue. The addictive properties of most of these drugs is a serious problem, however. (The three most widely used drugs in the world have addicting properties—caffeine, nicotine and alcohol.)

During the past decade many new kinds of behaviour altering drugs have been introduced with great success. They not only suppress manic excitement and anxiety, but also counteract depression and promote stability and imperturbability (2). The term "Ataraxia" has been introduced by Fabing to describe this altered mood which can be produced by drugs.

Because the practising anaesthetist is in daily contact with patients who have major physical problems together with a strong psychic overlay of anxiety or depression, it is of the utmost importance that he becomes familiar with the growing variety of mood altering drugs. This knowledge will ensure their employment in a rational manner, to the advantage of the patient and the anaesthetist. Frequent review of experimental and clinical evaluations of these new drugs should be the only basis for their use in general clinical practice. The efficacy of each agent must be coupled with a precise knowledge of its multiple actions and of its main dangers, together with information on the experiences of others (3, 4, 5).

GENERAL CONSIDERATIONS

The anaesthetist who is alert to psychosomatic relationships realizes that mood and behaviour are greatly modified by the physical condition of patients and by their environment (6). Insight is usually more readily secured in patients who

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have mental problems, if their nutritional and physiological status are satisfactory. The nutritional status in the geriatric patient and in any patient with a chronic illness always requires more careful attention, especially in relation to vitamin and protein intake (7). For optimum nervous stability certain vitamins such as thiamine, pantothenic acid, ascorbic acid and nicotinamide seem to be necessary. Psychotic states are often improved by large doses of these substances, which also seem to be important in preventing degenerative changes in the nervous system.

Studies of the action of the ataractic drugs have increased the knowledge of the role of serotonin (5-hydroxytryptamine) in nerve conduction, the activity of nervous tissue and in cardiovascular homeostasis. The suggestion is that optimum nerve function depends on the ratio of intracellular to extracellular serotonin. When there is a relative increase in intracellular serotonin, there is increased tension, alertness, irritability and a tendency towards convulsive behaviour. On the other hand, a relative excess of extracellular serotonin is associated with central nervous system depression and withdrawal. Serotonin may be the most important regulator of the activity of the subcortical areas of the brain (8, 9, 10). Its importance in brain function is indicated by the observation that serotonin is affected differently by the various types of tranquillizer. Reserpine releases serotonin from cells in the central nervous system, especially in the brain stem. On the other hand, chlorpromazine has been found to inactivate serotonin which has been injected or which is in the circulation; while mepazine does not affect serotonin in the circulation. Chemical considerations associated with serotonin and its chemical relatives suggest the importance of the blood-brain barrier in connection with the peripheral administration of some of these drugs. The blood-brain barrier is no specific structure but is a functional block to certain chemicals which seem to be easily dehydrogenated by brain cells as an adaptive protection to the organism as a whole. This barrier may be overwhelmed by overdosage. The physiological action of these chemicals suggest, also, the importance of feed-back to the central nervous system from the periphery, particularly of proprioceptive impulses from muscles and joints. This activity stimulates mental alertness and tension in much the same way as does hyperthyroidism (11).

Although the clinician cannot adequately control chemical and physiological factors in mental disturbance as yet, every attempt should be made to regulate the disturbing environmental factors. The ataractics can aid the anaesthetist to obtain a more satisfactory response to environment in mentally disturbed and psychoneurotic patients, as well as in those with the common anxiety response to operation (12, 13).

Differentiation of cortical neuroses into motor, sensory and mental forms is possible. Depending on the areas or structures of the cortex which are over-stimulated by impulse alterations in it, and in the hypothalamus and the thalamus, abnormal behaviour will differ in each individual. The determining factors depend on whether specific or non-specific discharges occur through cortical or subcortical structures of the brain. If abnormal discharges pass mainly through the sympathetic structures of the hypothalamus, a sympathetic or anxiety type

of neurosis appears. Such discharges through the parasympathetic system cause a different type of perturbance (peptic ulcer, spastic colon, etc.). These changes may be indicative of an altered balance of chemical substances in the brain (epinephrine, norepinephrine, serotonin, acetylcholine and histamine).

The primary role of ataractics in anaesthesia is to decrease the state of mental agitation, most probably by inhibiting in the subcortical reticular activating system the transmission of noxious motor, sensory and psychic stimuli to the cortex. They may also be effective by raising the threshold of response to reflex stimulation in the specific areas of the cortex, thalamus, hypothalamus, spinal cord, and certain highly sensitive reflex areas in other parts of the body (14). They also provide the physical and mental relaxation which is needed for development of "natural sleep." Present efforts to distinguish quantitatively and qualitatively the actions of the various drugs must proceed, therefore, in order to provide the clinician with a sound basis for the analysis of the areas of usefulness of each of the ataractics with particular reference to their effect on regulation of the autonomic nervous system.

The simplest approach to a review of these drugs is by classification according to their sedative activity. Insufficient data are available to present this with respect to the effect on endogenous serotonin. Two other approaches are available. One of these is based on the differentiation of sedation into hypnotic, psychotic and neurotic moieties (15). In this classification the hypnotic-sedative greatly depresses the cortex and thus raises the threshold of the nervous system to all sensory perceptions and enforces drowsiness and sleep (opiates, chloral hydrate, barbiturates). The psychosedatives help to control the agitation of psychotic patients and render disturbed patients more amenable to psychotherapy (reserpine, chlorpromazine, azacyclonol). The neurosedatives are useful mainly in anxiety and tension states associated with neurotic disturbances (ectylurea, meprobamate, hydroxyzine, bromides). This classification in man is hindered by the marked overlapping of effects and the knowledge that no two patients will respond alike to a sedative.

Another method of classification is the one most frequently used by the pharmacologist. It depends, primarily, on the structural formulae of compounds. This is usually the best way to separate the various compounds. For the purpose of this review the ataractic drugs will be divided into five groups, mainly on the basis of their chemical structure, but also with due regard to their primary mode of sedation, as it is not always possible to correlate the activity of a drug with its chemical structure (e.g., azacyclonol and pipradrol). The groups are as follows: (*a*) alkaloids of rauwolfia; (*b*) phenothiazine derivatives and analogues based on chlorpromazine; (*c*) benzhydrol derivatives; (*d*) hydroxypropane derivatives; (*e*) miscellaneous neuro- and hypno-sedatives. The pertinent clinical and pharmacological data will be discussed and summarized under the above headings. The structural formulae of these compounds are shown in Figure 1. The trade name, efficacy in anaesthesia, average dose for premedication in anaesthesia (for patients in the age group 15–60 years, and in physical state I and II) and important reactions or dangers are summarized in Table I.

TABLE I

Trade name	Official and chemical name	Anaesthetic indications (mg.)	Clinical dose	Dangers and reactions
		RAUWOLFIA ALKALOIDS		
Serpacil (Ciba) Sandril (Lilly) Quiescin (Organon)	reserpine	Not useful in anaesthesia due to delayed action Psychosedative		Hypotension
Moderil (Pfizer) Raudixin (Squibb) Rauwiloid (Riker)	Rauwolfia Alkaloidal Fractions	Acute psychosis with excitement Compulsive drives Hypertension	0.25	Suicidal depression
Harmonyl (Abbott)	Deserpidine II—desmethoxyreserpine	Tachycardia		
		DERIVATIVES OF PHENOTHIAZINE		
Largactil (Poulenc)	Chlorpromazine	Psycho and neurosedative, sympatholytic	50–100 (oral)	Hypotension
Thorazine (S.K.F.)	2 chloro-10-(3-dimethylamino-n-propyl)-phenothiazine hydrochloride	Nausea, vomiting, hiccoughs, pruritis Shivering Delirium Premedication Potentiate anaesthetics Prevent myocardial irritability Dilate coronaries Depress cardio-respiratory reflexes Facilitate hypotension and hypothermia Mild antisialogogue	25 (i.m.) 5– 10 (i.v.)	Tachycardia Skin allergy
Pacatal (Warner-Chilcott)	Mepazine 10-(N-methyl-3 piperidylmethyl)-phenothiazine acetate	Milder than chlorpromazine Anticonvulsant Parasympatholytic	100 (oral) 50 (i.m.) 25 (i.v.)	Hypotension
Sparine (Wyeth)	Promazine 10-(3-dimethylamino-n-propyl)-phenothiazine hydrochloride	Milder than chlorpormazine	100 (oral) 50 (i.m.) 10 (i.v.)	Hypotension
Stemetil (Poulenc) Compazine (S.K.F.)	Proclorperazine 2-chloro-10-(3-1-methyl-4-piperazinyl-propyl)-phenothiazine dimaleate	Anti-emetic Premedication Hypno and psycho sedative	10 (oral) 5 (i.m.)	Hypotension
Trilafon (Schering)	Perphenazine 1-(2-hydroxyethyl)-4-[3-(2 chloro-10-phenothiazyl-propyl] piperazine	Anti-emetic Premedication Hypno and psychosedative	10 (oral) 5–10 (i.m., i.v.)	None
Phenergan (Poulenc) (Wyeth)	Promethazine N-(2-dimethylamino-n-propyl) phenothiazine	Antihistaminic Hypno and psycho sedative Anti-emetic Antisialogogue	100 (oral) 50 (i.m.)	None

TABLE I (*continued*)

Trade name	Official and chemical name	Anaesthetic indications	Clinical dose (mg.)	Dangers and reactions
		DERIVATIVES OF HYDROXYPROPANE		
Myanesin (B.D.H.) Tolserol (Squibb)	Mephanesin 3-(2-methyl phenoxy)-1,2-propanediol	Muscle relaxant Pain due to muscle spasm Neurosedative in obsessional disorders	1 gm. (oral) 1 gm. (i.v.)	Nausea and vomiting Intravascular haemolysis Phlebothrombosis
Miltown (Wallace) Equanil (Wyeth)	Meprobamate 2-methyl-2-n-propyl-1,3-propanediol dicarbamate	Premedication Neurosedative in anxiety and tension states Muscle relaxation Hypnosis (somnolence)	800 (oral)	Skin allergy Addiction
Acalo (Lilly) Ultran (Lilly)	Phenaglycodol 2-p-chlorophenyl-3-methyl-2,3-butanediol	Premedication Neurosedative in anxiety and tension states Antispasmodic Anticonvulsant	600 (oral)	
		DERIVATIVES OF BENZHYDROL		
Levol (Horner) Suavitil (Glaxo)	Benactyzine hydrochloride B diethylaminoethyl benzilate hydrochloride	Premedication Neurosedative for psychomotor hyperactivity anxiety and tension states Antisialogogue Potentiate barbiturates	3 (oral)	None reported Contraindicated in depression and psychoses
Suvren (Ayerst) Covatin (Warner)	Captodiamine hydrochloride p-butylthiodiphenyl-methyl-2-dimethylaminoethyl-sulphide-hydrochloride	Premedication Neurosedative Psychosedative (depress irritability) Antispasmodic (smooth muscle) Potentiate barbiturates	100 (oral)	None reported
Atarax (Roerig) (Pfizer)	Hydroxyzine 1-(p-chlorobenzhydryl) 4- [2-(2-hydroxyethoxy-ethyl)] diethylenediamine dihydrochloride	Premedication Neurosedative for anxiety and tension states Antihistaminic	50 (oral) 25 (i.m.)	None reported
Frenquel (Merrell)	Azacyclonol alpha-(4-piperidyl)benzhydrol hydrochloride	Neuro and psychosedative for acute psychosis, toxic hallucinations, confusion and postoperative psychosis	10 (i.v.) (q 8 h)	None reported
Meratran (Merrell)	Pipradrol alpha-(2-piperidyl) benzhydrol hydrochloride	Psychomotor stimulant for post operative psychic depression	2 (i.v.)	Contraindicated in psychomotor agitation (danger of suicide)

TABLE I (*continued*)

Trade name	Official and chemical name	Anaesthetic indications	Clinical dose (mg.)	Dangers and reactions
Ritalin (Ciba)	Methyl-phenidyl acetate	Psychomotor stimulant Respiratory stimulant (analeptic)	30 (i.m.) 20 (i.v.)	Contraindicated in psychomotor agitation
	methyl-(alpha-phenyl-2-piperidyl)-acetate hydrochloride	Postoperative anaesthetic depression Morphine depression		
		MISCELLANEOUS SEDATIVES		
Hexamid (Nordmark)		Premedication Psychosedative	100 (i.m.)	?
	2,4,6-trioxohexahydro-5-diethylaminoethyl-pyrimidine	Potentiate anaesthesia Antisialogogue	50 (i.v.)	
Nostyn (Ames)	Ectylurea	Premedication Neurosedative for anxiety and tension	600 (oral)	None reported
	2 ethyl-cis crotonylurea			
Luminal (Winthrop Stearns)	Phenobarbital	Premedication (60 min. ante h.s.) Neurosedative	100 (oral)	Hangover excitement
	Sodium ethyl phenyl barbiturate	Hypnosedative Anticonvulsant		Skin allergy Nausea
Dormison (Schering)	Methylparafynol	Premedication (60 min. ante h.s.) Hypnosedative	500 (oral) 500 (i.m.)	Allergy Hepatotoxic?
	3-methyl-pentyne-ol-3	Anticonvulsant ?		Belching Bad after-taste Visual and speech disturbance
Placidyl (Abbott)	Ethylchlorvynol	Premedication (30 min. ante h.s.) Hypnosedative	500 (oral)	None reported
	Beta-chlorovinyl-ethyl-ethynyl-carbinol			
Valmid (Lilly)	Ethinamate	Premedication (30 min. ante h.s.) Hypnosedative	500 (oral)	None reported
	1-ethinyl-cyclohexyl-carbamate	Neurosedative		
Doriden	Glutethimide	Premedication (60 min. ante h.s.) Hypnosedative	500 (oral) 250 (i.m.)	Nausea Skin allergy
	alpha-ethyl-alpha-phenyl glutarimide			
Noludar (Roche)	Methyprylon	Premedication (30 min. ante h.s.) Hypnosedative	300 (oral)	None reported
	3,3-diethyl-5-methyl-2,4-piperidinedione	Neurosedative		

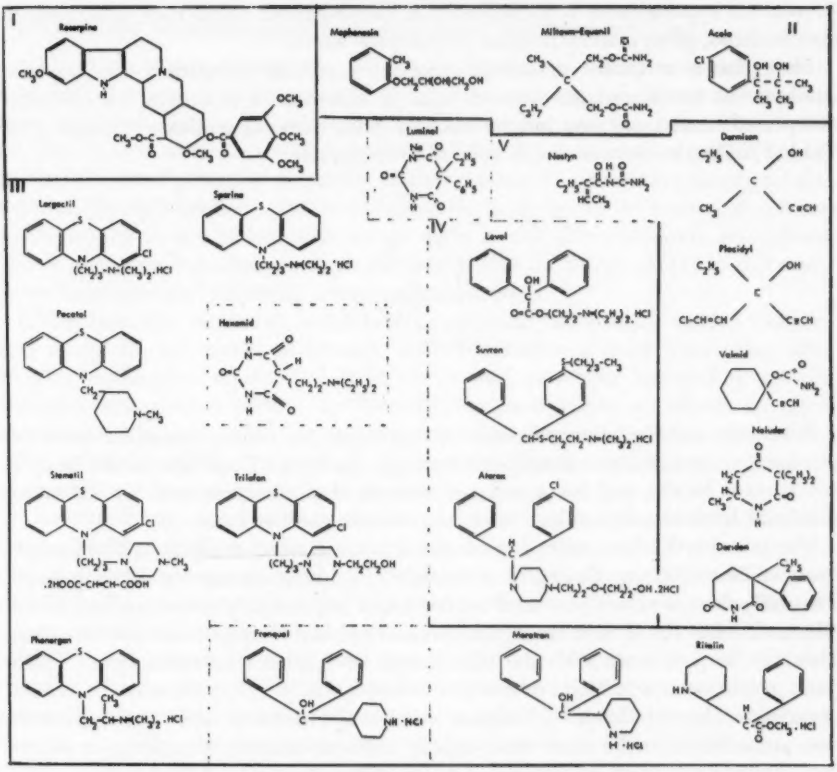


FIGURE 1. Comparative chemical structure of ataractic drugs.

DESCRIPTION OF DRUGS

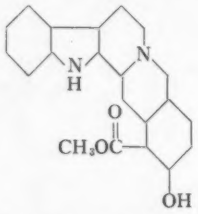
Alkaloids of Rauwolfia

The roots, leaves, and juice of rauwolfia plants were used from primitive times by the Hindus for relief of fevers, insomnia, dysentery, seizures and frenzy. The apocynaceous plant was named *Rauwolfia serpentina* in honour of Leonard Rauwolf who was a sixteenth-century botanist and physician. Modern pharmacological and clinical studies were reported from India beginning in 1931 (16, 17, 18). The Indians noted clinically that the powdered root of rauwolfia plants lowered blood pressure and quieted mania.

Reserpine is the most useful alkaloid of rauwolfia. It was isolated in 1952 by Schlittler and was found by Bein to have hypotensive and sedative action (19, 20). The first clinical reports on reserpine were published in 1954 (21, 22). Since then many clinicians have agreed on the value of reserpine as a hypotensive tranquillizing agent. The powdered whole root is also available as a tranquillizing agent for office practice and for producing a gradual, sustained lowering of blood

pressure in hypertension. It is claimed that the powdered whole root, satisfactorily standardized, gives activity not due to reserpine alone.

Reserpine is a white crystalline compound, soluble in alcohol and glycols, insoluble in water and sensitive to light in solution. It is a complex chemical compound containing an indole nucleus with several methoxy groups (see Table I). The structure is closely related to yohimbine:



Reserpine and the other alkaloids of Rauwolfia are readily absorbed from the alimentary tract and are distributed through the body. Their fate in the body is not known. Brodie and his associates indicate that reserpine acts by liberating serotonin from blood platelets, intestinal mucosa and the brain (9).

The powdered whole root of rauwolfia is administered orally in tablet form in doses of 50 to 100 mg. Reserpine is available in tablets containing 0.25 mg. each. The daily dose of reserpine varies from 0.1 to 1 mg., usually given orally. Clinical effects develop slowly but are significant and marked. Bradycardia develops first. This can be prevented with the solanaceous or synthetic antisialogogues (atropine, oxyphenonium). Blood pressure is reduced slowly in hypertension by central depression (hypothalamic?). Tension, emotional instability and over-aggressiveness are relieved at the same time, usually without causing drowsiness or sleepiness. No untoward effects are noted on the liver, kidney or blood cells. On the other hand, there may be nasal congestion and disturbance of appetite. Prolonged therapy may cause constipation. In some patients reserpine has been found to cause depression. *This may be serious enough to develop into suicidal tendencies.* Tolerance or addiction has not been reported. Allergic reactions are rare.

In office practice rauwolfia has been found to reduce complaints of dizziness, insomnia, excitability, irritability and anxiety. It may promote a sense of well-being among nervous individuals and reduce premenstrual tension and nymphomania. Outstanding has been the effectiveness of rauwolfia in anxiety and in hypertension associated with excitability. In all of these respects it is particularly useful in old people.

Its use should be carefully controlled clinically and its administration should be stopped promptly if depression or other untoward effects occur. If a surgical operation becomes necessary, it is well to discontinue therapy several days before the operation if general or spinal anaesthesia is to be used. If an emergency operation is required, 0.5 mg. of oxyphenonium and 5 mg. of methedrine may be administered intravenously before induction of anaesthesia. Because of the delayed onset of sedative action, this group of drugs has no specific place in clinical anaesthesia (23, 24, 25).

Phenothiazine Derivatives and Analogues based on Chlorpromazine

Chlorpromazine-hydrochloride was synthesized by Charpentier of Rhône-Poulenc Laboratories in France in 1951. The pharmacology of chlorpromazine has been widely studied in animals and in man during the past five years (26, 27, 28, 29, 30). It is a white crystalline powder, soluble in water with a pH of 5, and stable for a short period. It is quickly absorbed from the alimentary canal and distributed through the body. While its fate in the body is not yet known, it appears to be destroyed or eliminated in six or eight hours. The numerous side effects which may develop always follow prolonged use of the drug (31), and have never been recorded following a single administration.

Chlorpromazine depresses conditioned responses, antagonizes motion sickness and drug-induced emesis, depresses abnormal motor activity (shivering, hiccoughs, dyskinesia, myocardial irritability) and produces tranquillity in the delirious and agitated patient. Parenterally, the most important effects are peripheral vasodilatation, mild hypotension, transient tachycardia and reduction of reflex irritability. Chlorpromazine is slightly antihistaminic and relaxes the tone of smooth muscles and spasticity in striated muscles.

The anaesthetist must be wary of the orthostatic hypotension produced by this drug; and its potentiating effect on hypnotics, analgesics and anaesthetic agents calls for cautious management of anaesthesia. Body temperature is lowered slightly and a moderate to marked adrenolytic effect is evident when the drug is administered parenterally. When hypotension occurs, pressor drugs must be carefully selected (phenylephrine) and larger doses are required for an effective response. Pressor reversal effect occurs with epinephrine. It has no anticonvulsive action. The hypertensive action of serotonin is reduced by chlorpromazine (direct experiments show that chlorpromazine antagonizes serotonin). It also increases brain-stem content of adenosine-triphosphate. Tolerance seems to develop to chlorpromazine on repeated oral administration.

French investigators first noted the central depressive effects of chlorpromazine and its inhibition of psychic disturbances (32). Lehman and Hanrahan have published detailed accounts of the inhibiting effect of chlorpromazine on psychomotor excitement and manic conditions in man (33).

Clinical evidence shows the value of chlorpromazine in controlling nausea and vomiting due to a variety of causes, including drugs, radiation, pregnancy and motion sickness. In severe cases, effective control is quickly obtained by an intramuscular dose. For milder cases, or in children with viral gastritis, small oral doses every six hours may be satisfactory. If the drug cannot be tolerated orally by children, it may be given by rectal suppository.

Chlorpromazine is most useful in controlling psychomotor agitation. It may also relieve hallucinations and delusions in schizophrenia. In depressive states clear benefit is *not* usually observed. For improvement in psychotic patients, high doses usually seem necessary. This dosage should be reduced as soon as a beneficial effect is seen. In agitated senile patients small doses by mouth have been helpful.

Chlorpromazine relieves symptoms of several forms of dyskinesia (34); it some-

times helps also in controlling withdrawal symptoms in opiate and alcohol addictions. It has been used with great succcess as an adjunct to various analgesics in relieving the pain of cancer. In selected cases, chlorpromazine is useful as a preanaesthetic medication or as an adjunct to anaesthesia (35, 36, 37, 38). Preoperatively, it relieves anxiety, aids in controlling restlessness during spinal anaesthesia and reduces postoperative nausa, vomiting and delirium. It causes only slight reduction of salivary secretions (39). Chlorpromazine is very helpful in relieving persistent hiccoughs. It was also found to be of value in the conservative treatment of peripheral vascular disorders (40).

Undesirable effects of chlorpromazine are uncommon even when given orally or parenterally over a prolonged period. Its most unsatisfactory effect is the production of allergic reactions. This may even occur by contact sensitization among nurses or physicians. Fortunately, the allergic reactions clear promptly on stopping treatment or contact. In some patients, urticarial rashes may appear, while others may show gastrointestinal distress. An allergic-type of jaundice is the most serious untoward effect from chlorpromazine, but the incidence seems to be less than 1 per cent in patients on prolonged therapy.

The administration of chlorpromazine should be stopped on the appearance of any untoward symptom. It may usually be restarted safely after a week or so without any further untoward effect or allergic reaction. Chlorpromazine should not be used in the presence of liver disease and it is not wise to give it to a patient who is under the influence of hypnotics or alcohol. Patients requiring an operation and who are receiving chlorpromazine must be more carefully managed during anaesthesia. If the operation is elective, the drug should be discontinued a day before. If an emergency operation is required, physical measures should be employed to counteract the peripheral vasodilatation. For elective operations, fine judgment is required to select the proper dose for premedication (10-50 mg. intramuscularly) and for therapeutic measures during an anaesthetic (1-10 mg. intravenously) (41).

Mepazine (*Pacatal*®) was developed in Europe in 1953. It is a white crystalline salt which is photosensitive. It is rapidly absorbed following oral administration. The pharmacology of mepazine was first reported in 1954 (42). It is said to exert a selective regulatory action on the central nervous system, without inhibiting higher centres. The ability of mepazine to produce ataraxia without dulling of alertness is much milder than that of chlorpromazine. The most important effects of mepazine when used in pre-anaesthetic medication appears to be mild sedation without excessive soporific action, potentiation of anaesthetics and a balanced depression of the autonomic nervous system. Mepazine also depresses myocardial irritability, has moderate antipyretic properties, some anti-Parkinson effect, inhibits gastrointestinal contraction caused by acetylcholine or histamine, and has a mild mydriatic effect. It blocks effectively the salivary flow produced by pilocarpine, and decreases the pressor action of adrenalin, but does not act as a serotonin antagonist. Mepazine is said to have a relatively weak anticonvulsant effect against chemically induced convulsions.

In summary, the pharmacological actions of mepazine are similar to those of chlorpromazine, but its effects on the parasympathetic nervous system are greater

while all other effects are milder. Hence it causes less haemodynamic disturbance while ataraxia is adequate (43, 44, 45, 46). Aside from hypotension, no serious side effects have been prominent. Allergic and haematologic disturbances are likely to occur, however, if prolonged therapy with large doses is employed.

Promazine (*Sparine*®). The structural formula of promazine is identical to that of chlorpromazine, except that it lacks the chlorine atom in the 2 position. It is a crystalline salt that turns slightly pink on standing. In most respects the acute actions of promazine are the same as those of chlorpromazine but are less potent. The taming effect of promazine on monkeys is more predictable and consistent. This differs from that produced by chlorpromazine in that the taming is less masked by depression. Recovery from the effect of promazine is more rapid than with chlorpromazine because it is less potent. It has been found to control effectively symptoms of central nervous system excitation, to allay apprehension and anxiety and to calm the acutely agitated patient. It is indicated in the management of a variety of acute mental disturbances. It appears to be best suited for alcohol-induced inebriation syndromes such as delirium tremens, acute hallucinosis, acute tremulousness as well as agitation due to various psychoses, and for withdrawal symptoms of drug addiction (47). Promazine is not at the present time recommended for use in chronic mental disturbances, but may be used to control acute episodes of hyperactivity. Administration should be discontinued when these disturbances are under control (48, 49, 50).

Patients with delirium tremens respond as dramatically to promazine as to chlorpromazine: they become calm, more rational and in most instances sleep normally following a single intravenous dose. However, there is less likely to be serious vasomotor disturbance with promazine. Similar responses are obtained in patients with acute hallucinosis. When the acute phase is controlled by intravenous therapy, the patient may be maintained on oral or intramuscular doses until improvement persists (limit therapy to two weeks).

In acutely disturbed psychotics, the intravenous administration of promazine (25 to 50 mg.) controls the acute symptoms. The tranquil state is then maintained by oral or intramuscular administration. Sleep from which the patient can be aroused easily follows this treatment, and on maintenance therapy the patient remains quiet, calm and co-operative. Hallucinations when present are either abolished or become less frightening.

Side effects of promazine include drowsiness and transitory postural hypotension. Dizziness without marked change in blood pressure has been reported following its use in alcoholics, whereas with chlorpromazine there is frequently a marked hypotension. Allergic skin reactions, alterations in peripheral blood cells, hepatic dysfunction and extrapyramidal symptoms resembling Parkinson syndrome have been uncommon. Seizures are being reported with increasing frequency when high doses are taken. Cases of agranulocytosis have been recorded recently, but are as rare as with chlorpromazine.

As the use of this drug increases, the number of toxic reactions appear to be increasing, but they do not seem to be as numerous or as severe as for chlorpromazine. This may reflect a more conservative and cautious approach to intensive therapy based on the experiences with the latter.

The amount, route of administration, and frequency of administering chlorpromazine, mepazine, or promazine, should be governed by the degree of central nervous system excitation present and the patient's initial response. The oral route of administration should be used whenever possible, but when nausea, vomiting or lack of co-operation is evident the drugs should be given intravenously or intramuscularly. When given by these routes the patient should be closely observed until the peak action of their effect is subsiding. In general, doses of 50 to 100 mg. of mepazine or promazine are sufficient when given intravenously. If the desired calming effect is not apparent within 5 to 10 minutes, a smaller dose may be repeated. Once the desired effect is obtained the dose may be given intramuscularly or orally in 25 to 200 mg. doses at 4- to 6-hour intervals, depending upon the previous response of the patient. It is seldom necessary to administer more than 20 mg. of chlorpromazine intravenously for similar effects, as it is about twice as potent as mepazine and promazine.

Proclorperazine and perphenazine are aminophenothiazine derivatives with a wide range of activity. Because of their reported efficacy in both mild anxiety and severe psychotic reactions, they have been termed "broad spectrum tranquillizers."

Proclorperazine was developed by the combined effort of Rhône Poulenc Specia (Stemitil®) and S.K.F. Laboratories (Compazine®). It has been used for a wide variety of mental and emotional conditions (51): anxiety, agitation, agitated depression, tension, confusion, restlessness, senile agitation and post-alcoholic states. Anxious or agitated patients become calm on this medication. Tension is relieved and replaced by mental and physical relaxation. Patients become quieter and more co-operative, sleep soundly at night and remain alert during the day.

Proclorperazine was found effective when the presenting symptoms were both mental and emotional and when these psychic conditions complicated somatic disorders. It is five to ten times more potent than chlorpromazine. At the present time it is recommended for relatively short therapy (not longer than two weeks). In clinical trials, small doses administered orally have been found to be highly effective as a psycho- and neuro-sedative. It is also a potent anti-emetic in a wide variety of conditions (52)—pregnancy, viral gastro-enteritis, postoperative conditions, duodenal ulcer, terminal cancer, meningeal inflammation, radiation sickness, migraine and tension headaches. Side effects include mild drowsiness, some dizziness and mild skin reactions. Extrapyramidal symptoms are neither common nor severe and disappear upon withdrawal of the drug.

The potentiating action of proclorperazine is not as great as that of chlorpromazine. However, if sedative agents such as alcohol, opiates or barbiturates are used in conjunction with it, their amounts should be greatly reduced. Proclorperazine is contraindicated in comatose or greatly depressed states, and is probably best avoided in the presence of liver disease.

The dosage recommended for night sedation is 5 to 10 mg. by mouth and for preoperative sedation 5 mg. may be given intramuscularly one hour before anaesthesia.

Perphenazine (*Trilafon®*) was introduced by Schering Corporation. This phenothiazine derivative is about twice as potent as proclorperazine and ten to fifteen times more potent than chlorpromazine. It appears to be equally as

effective as an ataractic and an anti-emetic. The advantages claimed are that it does not cause hypotension in the geriatric patient, and does not produce allergic reactions, or alterations in liver function as frequently as does chlorpromazine (53). In anaesthesia it may be used for premedication as described for proclorperazine. A very potent anti-emetic effect is produced by 5 mg. intravenously without marked depression of blood pressure or respiration.

As for the other phenothiazine derivatives described, proclorperazine and perphenazine should be administered with discrimination and their use should be attended by careful and regular observation. Since they are potent phenothiazine derivatives, the patient receiving them should be under close observation for any signs of significant blood changes or other toxic manifestations. If extrapyramidal symptoms or haematologic changes appear, the drugs should be discontinued. Their potent anti-emetic action may mask signs of overdosage by other drugs (e.g., digitalis) or may obscure the diagnosis of conditions such as intestinal obstruction and brain tumour.

Extensive clinical trial is still required to prove whether these two agents have any advantage over other phenothiazine derivatives now on trial. Their employment in anaesthesia should be restricted to premedication in the anxious or agitated patient, and to use as an anti-emetic.

Promethazine (*Phenergan®*). One of the first aminophenothiazine derivatives to show great promise as a therapeutic agent was promethazine (54, 55). It is a white crystalline powder which is practically odourless. It is soluble in boiling absolute alcohol. Although promethazine was marketed in this country in 1950, it was not until 1954 that its great potential clinical value was recognized (56, 57). Since then an ever wider clinical efficacy has become evident, as this derivative has practically no disturbing side effects or toxicity in therapeutic doses (58, 59, 60, 61).

Promethazine has a wide range of therapeutic effects which are highly desirable in pre-anaesthetic medication. In addition to its potent antihistaminic activity (which is two to three times as great as any previous such agent marketed), it is an efficient hypnosedative, potentiates anaesthetic action slightly and has adequate activity as an anti-emetic and an antisialogogue (39). These actions are not accompanied by depression of vasomotor tone and reflex activity—which are considered to be undesirable effects of the other phenothiazine derivatives.

Promethazine promises to be acceptable for general use in pre-anaesthetic medication because it potentiates the sedative effects of small doses of barbiturates and meperidine, and has no significant effect on blood pressure homeostasis, pulse rate or respiration. Dose recommended is 100 mg. by mouth at bed time and 25 mg. intramuscularly preoperatively, combined with reduced doses of a barbiturate and scopolamine. In children excellent preoperative sedation is achieved with smaller doses (60). To date, promethazine remains the most efficacious phenothiazine derivative for use in anaesthesia premedication.

Derivatives of Hydroxypropane

Mephenesin (*myanesin®*). One of Berger's early contributions to our present knowledge of the ataractic drugs resulted from his studies of the glycerol ethers

in 1946 (62). Mephenesin, an aromatic glycerol ether, was clinically the most important drug in this group. This compound is an odourless white crystalline powder which dissolves poorly in water, but is freely soluble in ether and ethanol. When taken by mouth (elixir form), or injected intravenously in 1 to 2 gm. doses, rapid absorption and distribution occur. Selective depression in the subcortical brain stem and depression of spinal polysynaptic transmission is produced. This causes a marked decrease in skeletal muscle tone and spontaneous activity, without loss of consciousness or disturbance of mental activity. Mephenesin also protects against convulsions due to strychnine and against electroshock seizures. It does not affect voluntary motor power and sensation (63).

In clinical practice it is used to relieve muscle spasm, and as an adjunct to the treatment of acute anxiety states and obsessional disorders. However, it is sometimes dangerous to take by mouth as it produces anaesthesia of the oropharynx and may facilitate aspiration of food. Its use is limited also on account of its transient duration of action.

Its importance as a muscle relaxant in anaesthesia was short-lived, as it is not as efficacious as curare and related drugs now in use (64). Its present use is limited to treatment of muscle spasm and to behaviour disorders resulting from organic brain disease in children (65). The renewed interest in this drug, initiated by Berger, led to the synthesis of such important ataractics as meprobamate and hydroxyzine.

Meprobamate (*Miltown®*, *Equanil®*). Berger found marked sedative and muscle-relaxing effects from meprobamate (66). This drug has muscle relaxant actions similar to those of mephenesin, but of greater potency and longer duration. It also antagonizes strychnine and metrazol convulsions. It produces a reversible flaccid paralysis of skeletal muscle without affecting the heart, respiration or autonomic functions. Its action has been localized to the multi-neuronal reflexes. The clinical efficacy of meprobamate lies in its marked sedative action. The drug is ordinarily given in tablets each containing 400 mg., four times daily. When sedative effects are observed, the dosage should be reduced, and if improvement continues the drug should be withdrawn (67,68).

Meprobamate is useful as a sedative in anxiety, but is less effective in manic states. It is helpful as an adjunct to direct psychotherapy. It aids in clearing behaviour problems due to anxiety, conversion-hysteria and it is helpful in withdrawal symptoms of alcoholism. Meprobamate is not useful in the psychoses. It promotes restful sleep and general muscular relaxation without depression or hangover. It aids in clearing anxiety, tension-headache and neurogenic skin conditions or abdominal distress. It aids generally in reducing psychic tension, irritability and restlessness.

There are hazards which occasionally accompany the use of this drug, even on single administration (69). Hypersensitivity and allergic reactions, and acute non-thrombocytopenic purpura have been reported. These are probably quite rare. The increased frequency of such reports may be attributed to the very extensive and uncontrolled use of this drug.

Although meprobamate may be classed as an ataractic, its use should be restricted to patients with mild anxiety and emotional instability. In anaesthetic

practice it is of value when given alone for night time sedation (800 mg.) and for pre-anaesthetic sedation (400 mg. intramuscularly) combined with an antisialogogue (70).

Phenaglycodol (*Acalo®, Ultran®*) is a new chemical compound derived from butanediol which was synthesized recently in the Eli Lilly Research Laboratories. It is a stable compound which is relatively insoluble in water, but quite soluble in ethanol and oils.

This type of compound was found to possess anticonvulsant and hypnotic activity. During trials of this drug as an anticonvulsant in children it was noted that there was marked improvement in their behaviour problems. This led Slater and associates to further studies on animals, which revealed that it had muscular relaxing effects similar to those of mephenesin (intraneuronal blocking effect) (71). In animal studies the compound exhibited selective depressant activity on polysynaptic pathways at spinal and superspinal levels. It also caused sedation and depression of arousal responses similar to those produced by barbiturates. The depression of spontaneous activity and mental tranquillity was not accompanied by effects on respiration, blood pressure or the electrocardiogram. This indicated that the drug might be efficacious as an ataractic of the neurosedative type.

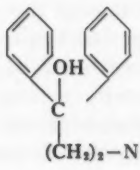
Reiten has compared the effects of phenaglycodol and meprobamate on psychological tests in human volunteers and patients (alertness, attention, reaction time, etc.) and found no adverse affect with either (72). This drug does not potentiate the hypnotic action of barbiturates nor does it produce a measureable or demonstrable relaxation of skeletal muscles in patients.

Clinical evaluations of this drug, which are in progress, indicate that it is of value for alleviating emotional tension without producing hypnosis. For pre-anaesthetic medication of the very tense patient, it may be of value in the dose of 600 mg. combined with a barbiturate at bedtime.

No contraindications or side effects of a serious nature have been observed with this drug to date. Mild nausea, dizziness and gastric irritation have been reported when it was used for daytime sedation. It has no cumulative action. Clinical trials indicate that it is useful in the treatment of alcohol withdrawal and in the management of patients with a predisposition to alcoholism. Extensive clinical evaluations of this drug have not yet been published.

Derivatives of Benzhydrol

Captodiamine hydrochloride (*Suvren®*). Weidmann and Peterson reported on the chemical and pharmacological investigation of 37 compounds which were closely related chemically to the antihistamine diphenhydramine hydrochloride (Benadryl®) (73).



These investigators were interested in this group of antihistaminic drugs because many of them exhibited potent sedative and hypnotic effects. Promethazine and diphenhydramine had previously been reported to have the most potent sedative-hypnotic activity in this class (74).

By changing the molecular structure, they were able to increase the sedative, and decrease the hypnotic and anti-histaminic actions. One of the compounds which they studied was captodiamine hydrochloride. They found the following pharmacological properties. It possessed sedative activity which was three to four times that of diphenhydramine and promethazine. The sedative action was believed to be mediated through the higher centres in the cortex of the brain. It also possessed a very potent spasmolytic or relaxing effect on smooth muscle. The action was like that of papaverine, but four to five times greater. It possessed no hypnotic effects, even in very large doses. It had no appreciable antihistaminic or anticholinergic effect, and did not cause hypotension.

No toxic effects on the haemogram have been reported. It has been tested in conjunction with several of the commonly used barbiturates and other hypnotics and does not produce a true potentiation of their activity. Captodiamine probably dilates the coronary vessels and exerts a powerful positive inotropic effect (increases the strength of muscular contraction) on the heart. The heart rate is unaffected. It has no affect on blood pressure or respiratory rate and does not possess any analgesic or anticonvulsant affects. It is particularly recommended for sedation in patients with anxiety, unrest and nervous tension when hypnosis is not desired, when long-term medication may be necessary and when smooth muscle relaxation without depressing normal tone of skeletal muscles is desired. This drug is not suitable for the treatment of severe psychosis. The dose recommended for night sedation is 50 to 100 mg. by mouth (75). Clinical evaluation in anaesthesia premedication has not yet been reported.

Benactyzine hydrochloride (*Levol®*, *Suavatil®*) was first described in Switzerland in 1936. In 1955 Jacobsen and others in Denmark found that it relieved anxiety in psychoneurotic patients (76, 77). Chemically it was closely related to diphenhydramine. It had a marked potentiating effect on general anaesthesia produced by intravenous barbiturates. It had a potent antispasmodic effect on the smooth muscle of the colon. Its anticholinergic action was found to be about twenty times that of chlorpromazine, and its antagonistic action to serotonin was approximately the same as that of chlorpromazine. As a histamine antagonist it was ten times less active than chlorpromazine and twenty times less active than diphenhydramine. It produced electro-encephalagraphic changes similar to those seen with atropine. Animal experiments show that it was dangerous to combine this drug with electroconvulsive shock treatment. It was found to have anticholinergic properties with a selective action on the hypothalamus. Its atropine-like action in man was mild. It appeared to raise the emotional threshold of the higher brain centres to irritant stimuli by blocking the nerve pathways to the hypothalamus, thus preventing reaction to external stimuli which normally cause strain and tension. It had no hypnotic activity. Serious toxicity has not yet been reported, but side effects—including dryness of the mouth and paralysis of accommodation—appear to occur frequently and are annoying (76).

Reports on its value in clinical medicine have been mixed. Some question its value in neuroses and in marked anxiety and tension. Others have reported it to be effective in anxiety, obsessional states, psychogenic asthma and eczema, alcoholic addiction and as an adjuvant to psychotherapy. It combines well with barbiturates and may be used in ambulant patients. The recommended dose is 1-3 mg. orally. It is most useful in diffuse non-specific anxiety and tension, and less so in phobias and hysteria. It is contraindicated in depression and psychosis (77, 78, 79, 80, 81). No reports have appeared regarding its use in premedication for anaesthesia.

Hydroxyzine (*Atarax®*) belongs to the group of mild ataractic agents (neurosedative). It contains a p-chlorobenzhydrol structure as do both chlorocyclizine —an antihistamine, and meclazine—an antinauseant. Hutcheon observed that intravenous injection of hydroxyzine causes a transient fall in blood pressure, an increase in coronary blood flow and suppression of epinephrine-induced ventricular arrhythmias. He also observed an inhibition of the pressor response to epinephrine in cats under pentobarbital anaesthesia (82). Hydroxyzine has been found to be a potent antihistamine and serotonin antagonist. It does not block the change induced in smooth muscle by acetylcholine and does not prevent histamine-induced depressor responses in anaesthetized animals. It markedly prolongs the sleep induced by intravenous barbiturates and prevents electroshock seizures, but does not prevent metrazol and strychnine convulsions. It appears to increase significantly the convulsant and toxic effects of strychnine. It does not antagonize hyperexciteability of tendon reflexes as does meprobamate. Changes similar to those produced after atropine occur in the electro-encephalogram. Rhesus monkeys treated with hydroxyzine respond with a disinterested state and catatonia similar to that seen with chlorpromazine and promazine (83).

In patients it produces a state of mental and physical relaxation, and relief from emotional tension (84, 85). No abnormalities in the blood or in kidney and liver function have been reported as yet. It has no significant effect on respiration, blood pressure or pulse rate. It is recommended in a dose of 25 mg. (intramuscularly) for premedication of surgical patients on the basis of its sedative and anaesthetic potentiating property.

Pipradrol and Azacyclonol (*Meratran® and Frenquel®*). Brown and Werner reported on the interesting actions on the central nervous system of some piperidyl-benzhydrol derivatives (86). These agents illustrate the importance of relatively slight changes in chemical constitution in determining significant differences in biological activity.

Pipradrol is a bitter crystalline compound which is relatively well absorbed from the alimentary canal. Its fate in the body is unknown. It seems to be destroyed or excreted within four to six hours. Its effects are chiefly on the central nervous system. According to Himwich it stimulates the central reticular substance of the brain. This is followed by cortical stimulation (87). Pipradrol does not increase blood pressure and has no effect on the gastro-enteric system or on respiration.

Since pipradrol is a general central nervous system stimulant, it has been used therapeutically to counteract mild depressive states and to counteract postanaes-

thetic and chlorpromazine depression (88). It apparently has no significant action on the autonomic nervous system and its use is not followed by wakefulness. It seems to be especially effective in the control of motor tic syndromes. Patients suffering from torticollis are often aided by treatment with pipradrol and it helps to relieve lumbar muscle spasm and low back pain. Its clinical value in these conditions is indicated by reports by Fabing and others (89, 90, 91).

No untoward side effects and no toxicity have been reported. The drug is administered orally in tablets each of 1 mg. 3 to 6 times daily. *It must never be given to a patient with psychomotor excitement, as this has led to suicide.*

Azacyclonol. In studying the action of related compounds, Fabing observed that the gamma isomer of pipradrol had quite different effects (92). In azacyclonol the nitrogen in the piperidine ring has been moved over two positions from that which it occupies in pipradrol. The resulting compound is a bitter white crystalline substance, partially soluble in water and rapidly absorbed from the alimentary tract. It is excreted or destroyed in four to six hours. This compound causes depression rather than stimulation of the central nervous system. It is in fact an antagonist of pipradrol, as well as of other central stimulating agents such as amphetamine or cocaine. Azacyclonol potentiates the depressant action of hypnotic and analgesic drugs. It is itself a relaxing agent and has insignificant toxicity on single administration (93).

Clinical trials indicate that azacyclonol is useful in acute schizophrenic conditions. It has an antagonistic action in model psychoses produced by lysergic acid diethylamide or by mescalline. The name Frenquel was given to it because of its ability to quell frenzy (92).

Azacyclonol may be useful in controlling the symptoms of acute schizophrenia and toxic hallucinations in a dosage of 10 mg. intravenously every 8 hours. It is not helpful in chronic schizophrenia or in senile or alcoholic patients with hallucinations, unless it is combined with other forms of drug therapy. Azacyclonol has no effect in depressive states or in obsessive-compulsive disorders. It does not aid in handling anxiety conditions (94).

Both pipradrol and azacyclonol require much more extensive study under controlled clinical conditions in order to indicate clearly their usefulness. In relation to anaesthesia, pipradrol may be of value in the management of severe psychic depression, whereas azacyclonol may be of value in the initial control of marked confusion and agitation in the postoperative period.

Methylphenidylacetate (*Ritalin®*). Meier has developed another interesting behaviour-altering drug which has the generic name methylphenidylacetate. It is a white crystalline compound soluble in water with a pH of 3 in 10 per cent aqueous solution. It is quickly absorbed from the alimentary canal. Methlyphenidylacetate is a central nervous system stimulant similar to pipradrol. Doses of 1 mg./kg. in experimental animals cause an increase in spontaneous activity with maximum restlessness in about an hour and with gradual recovery without untoward effects in about two hours. Against short-acting barbiturates it has an analeptic effect and counteracts respiratory depression due to morphine. There is little action on smooth muscles, on the cardiovascular system, or in circulating blood. No toxic effects have been observed (95).

It has been used in treating reserpine-induced depression and for markedly deteriorated chronic schizophrenic patients. Many showed significant clinical improvement. No untoward effects were noted and there was no interference with sleep (96, 97, 98). Its main value in anaesthesia is in the treatment of respiratory depression due to narcotic-analgesics and postanesthetic depression.

Miscellaneous Sedatives

Hexamid. Clinical trial with hexamid, a barbiturate acid derivative prepared by Nordmark Werken in Germany, has shown that this substance is not hypnotic, but possesses ataractic qualities similar to that of chlorpromazine. In animal experiments it was found to have half the toxicity, but a slightly greater duration of action than chlorpromazine. This drug has analgesic, anticonvulsant and antisialogugue properties, but has no significant effect on the circulation, respiration, body temperature or blood coagulation. When injected subcutaneously it produces local anaesthesia.

Subcutaneous and intravenous injections of 25 to 50 mg. have similar affects in man. These appear in about five minutes with subcutaneous injection and in one minute after intravenous injection, and are: dryness of the mouth, a feeling of warmth, lack of power of concentration and initiative, flight of ideas, a feeling of well-being (sometimes euphoria) and a decrease in sensitivity to pain. The response lasts for one to one and one-half hours. There is also a variable decrease in accommodation, accompanied by diplopia, and difficulty in speaking and calculating. The pulse rate falls about 20 to 25 per cent, but the blood pressure remains unchanged. The respiratory rate and amplitude are not affected and there is a minimal decrease in vital capacity. Muscular power, as measured by the dynamometer, is reduced 10 to 15 per cent. Hexamid, in the same dosage and by the same route of administration, has a shorter and somewhat milder action than chlorpromazine, particularly as far as the patients' initiative and ability to concentrate are concerned. The sensitivity to pain is reduced to about the same extend by both drugs and reduction in muscular power is about the same. Hexamid dries salivary secretion to a greater extent, the feeling of well-being is more marked and it causes bradycardia rather than the tachycardia seen with chlorpromazine.

Hexamid is more potent than mepazine, particularly in its sedative and antisialogogue properties. Its effect on the circulation is the same as mepazine. Unlike chlorpromazine and mepazine, it has no anti-emetic effect.

Hexamid appears to have a wide therapeutic margin. Five times the usual dose (250 mg. intramuscularly) causes light sleep and amnesia for the period of premedication, and anaesthesia is without other disturbance. The recommended dose of hexamid is as follows: for premedication 50 to 100 mg. subcutaneously or intramuscularly one hour before operation. This is combined with the usual doses of meperidine, but the belladonna derivatives are omitted. No toxic effects have been reported as yet. Hexamid is compatible with all anaesthetics and ancilliary drugs (99).

Ectylurea (*Nostyn®*) is an ataractic which was investigated by Pindell and associates in 1953 (100), and introduced clinically by Ferguson in 1956 (101).

It relieves everyday apprehension and anxiety in a wide dose range without impairing mental alertness or producing drowsiness or hypnosis.

This drug is an almost insoluble, white, crystalline compound prepared by dehydrobromination of carbromal. It is readily absorbed from the alimentary tract. Sedation with this drug occurs in 15 to 30 minutes and last several hours. Only in a very large dose does this drug produce sub-hypnosis or a state of profound depression. Its wide dose range between sedation and hypnosis indicates a much greater margin of safety than with existing sedatives. Caffeine given before or after this drug does not alter its sedative effect. It does not slow respiration beyond that seen during sleep and there is no effect on blood pressure or pulse rate. It has no anticonvulsant, analgesic or antispasmodic activity.

Ectylurea is recommended as a mild neurosedative (300-600 mg. at bedtime) which relieves tenseness and anxiety without causing depression, drowsiness or motor incoordination. Much larger doses are used for the management of psychotic patients. This produces more potent effects than meprobamate, but is less effective than reserpine or chlorpromazine. Toxic reactions have not yet been reported with long-term therapy.

Phenobarbital Sodium (*Luminal®*) and other barbiturates. Barbituric acid derivatives have enjoyed great popularity for premedication for many years because of their great efficacy as sedative-hypnotics and anticonvulsants. The large number of side effects which accompany the use of these drugs has led to their gradual replacement by other agents.

The most commonly used barbiturate derivatives for pre-anaesthetic medication are phenobarbital, pentobarbital and secobarbital. Natural idiosyncrasy often occurs. This is marked by hangover, inebriation, excitement or neuralgic-type pain. Excessive hypnosis, lassitude, nausea and vomiting and diarrhoea are frequent. One-third to one-fourth of the hypnotic dose usually produces sedation, but it is difficult to predict as this response is variable in the individual patient. These drugs should not be prescribed without an analgesic in the presence of pain as the patient usually responds with excitement and delirium instead of tranquillity. Psychoneurotic patients, especially, tolerate this type of sedation poorly. Many patients are allergic to the barbiturates and respond with swelling of the face or erythematous dermatitis. Addiction to barbiturates is relatively common and may be difficult to detect. Patients with renal or liver disease should not be given the barbiturate derivatives, which depend on these organs for degradation and excretion. Non-specific contraindications to barbiturate sedation include fever, hyperthyroidism and heart failure (102, 103).

Barbiturates are usually given as a 100 mg. oral capsule for a pre-anaesthetic hypnotic, and may be repeated by intramuscular injection one hour before induction of anaesthesia. Secobarbital and pentobarbital are also given intravenously as a sedative-hypnotic during regional anaesthesia. They are also used as an intravenous anaesthetic supplement for hypnosis, but they are unsatisfactory for this purpose as the patients tend to sleep far too long (35).

Methylparafynol is an unsaturated aliphatic carbonal (104) which was introduced by the Schering Corp. It is an orally potent, quick-acting hypnotic with anticonvulsant properties (105). It induces natural restful sleep from which

patients awaken alert and refreshed without drug hangover. Methylparafynol produces no respiratory depression and may be used in the presence of cardio-respiratory and broncho-pulmonary disorders when barbiturate hypnotics are contraindicated. Dosage recommended is 500 mg. by mouth, 15 minutes before sleep.

No adverse effect on the blood, kidney or liver function has been reported. Because of a potentiating effect, methylparafynol should not be given with large preoperative doses of barbiturates. Numerous physical and mental disturbances have been reported with this sedative. An unpleasant breath and after-taste also follows ingestion. Reports indicate that it is a satisfactory sedative in the young and in the aged, but it should be used with some caution as a few cases of poisoning have been reported (105-109).

Ethylchlorvynol (*Placidyl®*) is a new non-barbiturate hypnotic of tertiary unsaturated carbinol which was recently introduced by the Abbott Laboratories. This drug was the most active of a series of chlorinated carbinols with sedative effects (110, 111). It is said to exhibit a hypnotic effect superior to that of the unhalogenated acetylenic carbinols. The drug has special usefulness for ordinary insomnia due to tension, mild anxiety, mild excitement or agitation. For pleasant induction of sleep at bedtime the usual dose is 500 mg. This dose induces sleep in approximately 15 to 20 minutes, with an average duration of about 5 hours. When patients are awakened from sleep, they are alert and mentally clear and have no ataxia, nervousness, drowsiness or hangover. There are apparently no haematologic or liver function changes during administration of ethylchlorvynol. There are no observed effects on the pulse, blood pressure, respiration, blood or urine. There are no reports available of its clinical use for anaesthetic premedication.

Ethinamate (*Valmid®*), which was introduced by Eli Lilly Research Laboratories in 1953, is also a non-barbiturate hypnotic derived from tertiary unsaturated carbinol. The primary indication for this drug is simple insomnia caused by mental unrest, excitement, worry, apprehension, or extreme fatigue. Ethinamate is recommended for persons who are hypersensitive to barbiturates, and also, because of its very short action, for patients who awaken in the early morning hours and cannot get back to sleep. The usual dose is 500 mg. taken 15 to 20 minutes before retiring. The duration of sedation with this dose is about half that of secobarbital. Ethinamate has caused no demonstrable effects on the brain, blood, liver, kidneys or other body organs. It does not cause halitosis, nausea or skin rash.

Ethinamate should not be employed alone for insomnia due to pain, severe itching or coughing. It does not potentiate analgesics or other sedatives, and in a hypnotic dose it does not affect the blood pressure, pulse rate or respiration. No allergic manifestations or serious toxic reactions have been reported (112, 113).

Glutethimide (*Doriden®*), which was introduced by Ciba Pharmaceutical Products, Inc., is an oral non-barbiturate hypnotic-sedative. In the past few years it has become the most widely used sedative of this group. It is not soporific when given as a sedative and seldom causes morning hangover when given as a nighttime hypnotic (114). When given for insomnia its onset action is 15 to 20 minutes,

and it provides 4-8 hours of sound dreamless sleep. It is well tolerated by elderly neuro-psychiatric patients and by those with cardiovascular disease in whom the barbiturate sedatives may be poorly tolerated or contraindicated (115). It does not cause respiratory depression or alter blood pressure or pulse rate in therapeutic dosage (250-500 mg.). Prolonged administration has no effect on the blood picture or liver function (116). A number of suicides have been reported. In these cases 10 gm. or more were taken (117, 118).

One gm. given the night before and repeated one and a half hours before anaesthesia gives satisfactory sedation. Short-term administration does not cause gastro-intestinal or other disturbances. Skin rashes have been reported after prolonged administration.

Methyprylon (*Noludar®*), introduced by Hoffman-La Roche, Inc., is a non-barbiturate sedative hypnotic, derived from piperidine dione (119). Extensive clinical trials indicate that it provides relief of insomnia in approximately half an hour, and restful sleep continues for an average of six to seven hours (120-124). After this sedation, the patient generally awakens refreshed without lethargy or hangover. It is particularly recommended for relief of nervous insomnia as it causes a mild central depression (125). It is also useful for daytime nervous tension. When sleeplessness arises from pain, methyprylon should be given in conjunction with an analgesic.

The recommended dose for premedication is 300 mg. half an hour before retiring. No alteration in blood pressure, pulse rate or respiration occurs, and the prolonged administration of large doses did not produce toxic effects on the blood (126, 127). Gross overdosage, however, leads to fatal poisoning (128).

Comments

The most important information for the anaesthetist who employs these new drugs is first; the potency, range of activity, effect on vital signs and the incidence of allergic reactions for each compound. This knowledge will assist in the selection of dosage for a particular situation. Secondly, the ability of the compound to potentiate the sedative, hypnotic, analgesic or muscle relaxant activity of other drugs employed in anaesthesia; and thirdly the variability of effect to be expected with each compound—since the effect of some drugs shows a narrow range of response while most drugs are notorious for the great variation of individual response even in healthy subjects (129).

Knowledge of these points will be helpful in predicting whether a particular dose is likely to produce the desired effect, or undesirable side effects and toxic reactions. It will also assist the anaesthetist to avoid what are frequently termed hypersensitivity or idiosyncratic reactions but are in reality the effects of overdosage.

The use of ataractic drugs in the form of a "cocktail" in anaesthesia has been criticized during the past few years. It is the writer's opinion, and this is shared by many, that the new therapeutic agents should not be administered in combinations until precise knowledge of their actions, and wide experience in their use has determined the efficacy of each constituent. Advantage may be taken then of

combining these drugs for some more desirable effect. It must be recognized, however, that the toxicity of drugs is usually increased when they are used in combination (130). On the other hand, the combination of homeopathic doses of several drugs in order to provide broad action and to reduce the undesirable effects of the individual compounds results in an apparent reduction of their over-all efficacy. (131) Another action of many of these drugs to be considered is that they are capable of producing conditions such as allergy, while at the same time they are of value in the treatment of similar diseases (132, 133).

The many reports on the physiological and pharmacological responses to the ataractics are providing us with an insight into the specific effects of these agents on the heart and circulation, on the lungs and respiration, on the functions of the nervous system, and of other vital processes. These must be supplemented extensively in the immediate future.

These agents now can assist us in approaching an ideal in anaesthesia in which the patient may be permitted to have a restful, undisturbed period of sleep the night before an operation provided by a hypnotic drug which has a moderately rapid onset of action, lasts 6-8 hours and has no "hangover" effects. On the morning of operation, he may be rendered ataraxic for preoperative preparation. When all is ready, sedation, sub-hypnosis or deep sleep can be induced smoothly, without subjective discomfort and with minimal physiological disturbance. The period of operation can be managed by appropriate drugs to maintain light hypnosis, and to provide sufficient analgesia, muscle relaxation and reflex suppression during the operation. Postoperatively, the effects of the hypnotic and muscle relaxant drugs may wear off promptly while light analgesia, ataraxia, and depression of the vomiting centre may persist for several hours, or until the acute disturbances caused by anaesthesia and surgical trauma have subsided.

This state of affairs would be ideal, if attainable. By a careful selection from the wide array of drugs which are now available, this state can indeed be provided. The anaesthetist must learn to recognize anxiety and apprehension in his patients, even when these are not evident from overt behaviour or from changes in physiological parameters (pulse rate, blood pressure and character of breathing). He must then produce a controlled differential disintegration of the nervous system (134) that will prevent many of the serious endocrine and metabolic disturbances caused by anxiety and by anaesthesia which worried Wesley Bourne a generation ago, and have troubled all anaesthetists since; thus avoiding the inception of deleterious body changes in the period of surgical convalescence which are currently under extensive study by Francis Moore and many others (135-139) (see Fig. 2).

Anaesthetists occasionally "try" new drugs in clinical anaesthesia in an uncritical manner and without detailed knowledge of their pharmacology and of what to expect with human administration. On the other hand, there are those who stand pat with existing agents and hurl criticism at those who wish to employ the newer therapeutic drugs. There are two guiding rules which would be helpful to both groups. The first is the most honourable test of starting with yourself. One quickly learns the dose-response of a drug in this way. Osmond states that this test helps us as nothing else can to assess the value of verbal and published

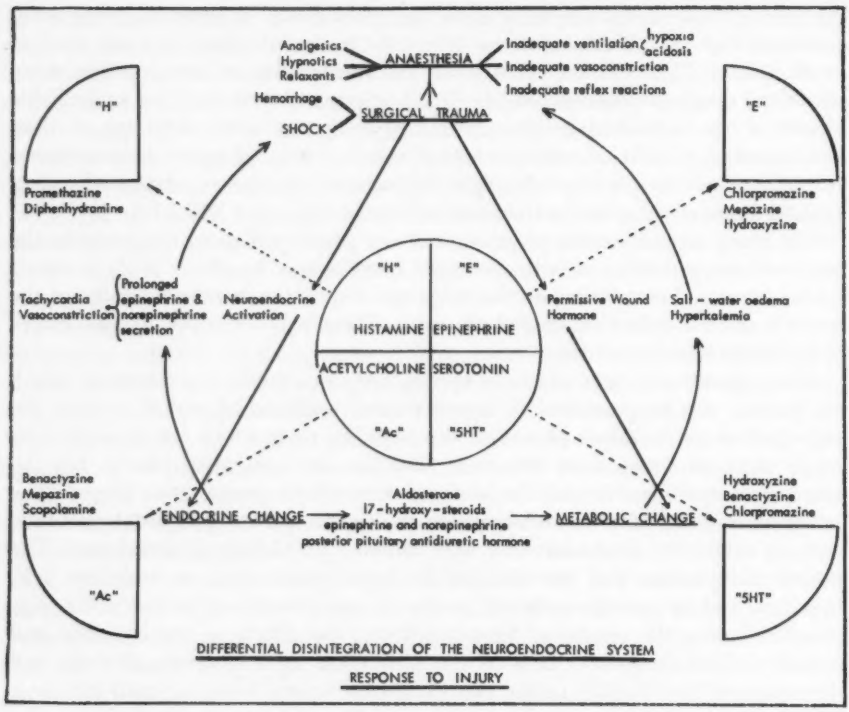


FIGURE 2. Schematic outline of manner in which ataractic drugs may block, under controlled conditions, the deleterious effects of anaesthesia and surgical trauma on the "normal" endocrine reactions which promote wound healing. The reactions usually observed after surgical trauma are: (*a*) corticosteroids are elevated in the blood; (*b*) *aldosterone production* is increased--and is elevated in the urine; (*c*) catecholamines are elevated in the blood; (*d*) antidiuresis occurs--patient cannot excrete water without solute.

reports and permits a more critical analysis of them (140). This method is especially useful with psychotherapeutic drugs. The second is that recommended by Noseworthy (141):

We should take every opportunity not only of watching others at work, but also of noting the subsequent condition of their patients. If we then honestly believe that our own results would have been the same, or better, well and good for the moment. If, on the other hand, we recognize that our own efforts do not stand up to such a comparison, three honourable courses are open to us: *aut disce*—either we can learn such techniques, perhaps even evolving something better; *aut discede*—or we can retire gracefully without regret or crabbed criticism; *maret sors tertial caedi*—there remains a third course, acknowledging our own shortcomings, we can help and encourage others —not to return, but to take stock and advance.

By following these recommendations, better insight into the role of ataractics in anaesthesia can be determined and their evaluation may be continued safely on a wide scale. The most reliable and valid way to evaluate these drugs further is to substitute them for the "routine" agents now in use, rather than to employ

them in conjunction with or as adjuvants to the older drugs. The experience accumulated during the next few years may then provide us with an objective and reliable assessment of them so that their efficacy, dangers and disadvantages may be classified.

Résumé

Au cours de la dernière décade, nous avons été témoins de l'apparition, avec grand succès d'ailleurs, de nombreux médicaments capables de modifier l'attitude des gens qui prennent ces médicaments. Non seulement, ces médicaments peuvent faire disparaître l'excitation et l'anxiété, mais encore ils peuvent enrayer la dépression et rétablir la stabilité et l'imperturbabilité (2). Fabing a suggéré le mot "ataraxique" pour décrire ce changement d'attitude produit par des médicaments.

Pour l'anesthésiste qui entre en contact quotidien avec des malades qui ont, en même temps, des problèmes physiques de grande importance et un état psychique empreint d'une grande anxiété ou d'une profonde dépression, il devient très important qu'il voit clair dans cette affluence toujours croissante de médicaments pouvant influencer l'attitude de ceux qui les consomment. La connaissance de ces médicaments ne fera qu'en rendre l'emploi plus judicieux pour le bénéfice du malade et de l'anesthésiste. L'examen répété des épreuves cliniques et expérimentales de ces médicaments devrait constituer la seule base pour justifier leur emploi en clinique. L'efficacité de chacune de ces drogues doit demeurer soumise à la connaissance précise de ses actions multiples et de ses principaux dangers, renseignements qui nous sont procurés par les expériences des autres (3, 4, 5).

En anesthésie, la première fonction des ataraxiques est de diminuer la tension nerveuse, très probablement en inhibant, dans la substance reticulée souscorticale, la transmission ou cortex d'influx nuisibles, moteurs sensitifs ou psychiques. Il est également possible qu'ils agissent en élevant le seuil da la réponse réflexe à une stimulation dans des zones spécifiques: le cortex, le thalamus, l'hypothalamus, la moelle épinière et certaines zones sensitives hautement réflexogènes de l'organisme (14). Ils procurent également un état de détente physique et psychique nécessaire à l'induction du "sommeil naturel". En conséquence, pour préciser quantitativement et qualitativement l'action de ces médicaments, nos efforts devraient tendre à procurer au clinicien une échelle pour l'évaluation des limites d'utilité de chacun des ataraxiques avec une mention spéciale de son pouvoir d'action sur le système nerveux autonome.

Dans la Figure 1, on peut prendre connaissance des formules développées de chacun de ces composés. On a résumé dans la Table I: le nom commercial, l'efficacité en anesthésie, la dose moyenne pour la prémédication en anesthésie (chez les malades de 15 à 60 ans dont l'état de santé est de risque 1 ou 2) ainsi que les réactions importantes et les dangers.

Le renseignement essentiel à apporter à l'anesthésiste qui emploie ces médicaments doit concerner d'abord: la puissance du médicament, les limites d'action, ses effects sur les signes vitaux et la fréquence de ses réactions allergiques. Ces renseignements sont précieux pour décider de la dose dans une situation donnée. Ensuite, l'anesthésiste doit être renseigné sur la possibilité de la drogue en question à potentialiser les autres médicaments employés en anesthésie: sédatifs, hypnotiques, analgésiques ou myorésolutifs; en troisième lieu, il doit être

renseigné sur les modifications d'action possibles de chacun des médicaments car l'effet de certains médicaments n'offre qu'une marge étroite dans leur réponse tandis que la plupart des médicaments sont reconnus pour apporter une grande variété de réponses individuelles même chez les sujets en santé (129).

La connaissance de ces détails deviendra précieuse pour prédire si une dose donnée saura produire l'effet désiré ou donnera des réactions toxiques et des effets indésirables. Elle permettra également à l'anesthésiste d'éviter ce qu'on appelle fréquemment de l'hypersensibilité ou de l'idiosyncrasie, et qui n'est, en réalité, que le résultat d'un surdosage.

Au cours des dernières, années, on a critiqué ce qui se pratique en anesthésie: l'emploi des ataraxiques sous forme de "cocktail." C'est l'opinion de l'auteur, opinion qui est partagée d'ailleurs par un grand nombre, que les agents thérapeutiques ne devraient pas être employés en associations avant qu'une connaissance précise de leurs actions et une grande expérience de leur usage aient précisé l'efficacité de chacun des composants de l'association. C'est alors qu'il peut y avoir intérêt à associer ces médicaments pour accroître l'effet désireé. Il faut se rappeler, toutefois, que la toxicité des médicaments augmentent habituellement quand on les emploie en associations (130). Par contre, l'association de doses homéopathiques de différents médicaments, pour obtenir une action plus vaste et diminuer les effets nuisibles des divers composants, entraîne une diminution de l'efficacité totale (131). Il faut également retenir que plusieurs de ces médicaments possèdent un autre pouvoir: celui de provoquer des états comme l'allergie tout en possédant, en même temps, une certaine valeur pour lutter contre de semblables maladies (132, 133).

Les nombreux résultats d'études sur la physiologie et la pharmacologie des ataraxiques nous permettent de jeter un coup d'œil sur le mécanisme intime d'action et sur les effets spécifiques de ces agents sur le cœur et la circulation, sur les poumons et la respiration, sur les fonctions du système nerveux et sur les autres processus vitaux. Dans l'avenir, il faudrait accroître et étendre ces études.

Ces drogues peuvent nous aider à atteindre un idéal en anesthésie, idéal qui consisterait à procurer, au malade qui doit être opéré le lendemain, une nuit complète et reposante en lui faisant absorber un hypnotique à action assez rapide, à durée d'action de 6–8 heures, ne possédant aucun effet indésirable. Le matin de l'opération, le malade pourrait être mis en état d'ataraxie pour la préparation préopératoire. Puis, quand tout serait prêt, on pourrait procurer soit une sédation, soit un sommeil léger, soit une sommeil profond avec un minimum d'ennuis personnels et de désordres physiologiques pour le malade. Durant l'opération, il faudrait posséder un choix de médicament permettant de maintenir un sommeil léger, de procurer une analgésie suffisante, un relâchement musculaire convenable et la suppression des réflexes nuisibles. Après l'opération, il faudrait que les hypnotiques et les myorésolutifs soient métabolisés rapidement tandis que les effets des analgésiques, des ataraxiques et des dépresseurs du centre des vomissements se prolongent pendant plusieurs heures ou jusqu'à ce que cessent ou disparaissent les ennuis causés par l'anesthésie et le traumatisme chirurgical.

Voilà ce qui serait l'idéal, s'il est possible de l'atteindre. Actuellement, en faisant un choix judicieux des médicaments à notre disposition, il est possible de procurer cet état. L'anesthésiste doit apprendre à dépister, chez ses malades,

l'anxiété et l'appréhension, même si elles sont masquées par de la fanfaronnade en s'aidant des modifications physiologiques (rythme cardiaque, tension artérielle et le type de respiration). C'est alors que l'anesthésiste doit exécuter une dissociation différentielle du système nerveux du malade (134) qui pourra prévenir de sérieux troubles métaboliques et endocriniens causés par l'anxiété et l'anesthésie, ce qui inquiétait Wesley Bourne il y a une génération et qui n'a cessé de laisser perplexes tous les anesthésistes depuis ce temps. On évitera ainsi l'installation du changements nuisibles dans l'organisme au moment de la convalescence chirurgicale, changements qui font l'objet d'une étude extensive par Francis Moore et d'autres (135–139) (voir fig. 2).

Il y a des anesthésistes qui, à l'occasion, emploient des nouveaux médicaments en anesthésie clinique et, cela, sans esprit critique, sans connaissance précise de leur pharmacologie et sans expectative précise de leur administration à l'homme. Par contre, il y en a d'autres qui suivent les sentiers battus avec les agents connus et ne craignent pas d'adresser des critiques à ceux qui désirent employer des médicaments plus nouveaux. Il y a deux lignes de conduite qui pourraient être utiles aux deux groupes: la première est l'épreuve la plus honorable: faire la première épreuve sur eux-mêmes. De cette façon, un individu apprend rapidement la dose-réponse d'une drogue. Osmond affirme que cette épreuve est plus précieuse qu'aucune autre pour apprécier la valeur des résultats verbaux et publiés sur le sujet et que cela en permet en même temps une analyse plus critique (140). La seconde ligne de conduite est dictée par Nosworthy (141):

> Nous ne devrions pas manquer une occasion de regarder travailler les autres, mais aussi de suivre l'évolution de leurs malades. Si, en toute honnêteté, nous avons la conviction que nos résultats auraient été les mêmes, ou meilleurs, à la bonne heure pour le moment. Si, par contre, nous réalisons que nos efforts ne supportent pas une semblable comparaison, il y a trois issues honorables qui s'offrent à nous: *aut disce* — ou nous pouvons apprendre ces techniques et peut-être en réaliser des meilleures; *aut discede* —ou nous pouvons abandonner, avec grâce, sans regret ni critique; *maret sors tertial caedi* — il reste une troisième issue: tout en reconnaissant notre insuccès, nous pouvons aider et encourager les autres — non pas à reculer mais à s'armer et à avancer.

En suivant ces conseils, nous obtiendrons une meilleure connaissance du rôle des ataraxiques en anesthésie et nous pourrons en continuer, en toute sécurité et sur une haute échelle, les applications cliniques. La façon la plus certaine et la plus objective d'étudier ces médicaments est de les substituer aux agents de "routine" dans le moment plutôt que de les associer ou de s'en servir comme adjuvants aux anciens médicaments. L'expérience que nous acquérerons durant les années à venir peut nous apporter des arguments fiables et objectifs et nous permettre d'en préciser l'efficacité, les dangers et les désavantages.

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BRONCHOSPASM: A CASE REPORT

JOHN W. DALES, M.A., M.D.[1]

BRONCHIAL SPASM, when it occurs during the course of a general anaesthetic, is often an error in technique, the cause of which should be immediately detected and corrected. Difficult ventilation results from spasm of the bronchi accompanied by a fixation of the chest wall. When muscular fixation of the chest predominates, ventilation can be improved by deeper anaesthesia or muscle relaxants. The bronchial component can be caused by insufficient anaesthesia, respiratory tract disease and certain drugs. Thiopentone, cyclopropane, and d-tubocurare may cause bronchospasm by their histamine-like action. Pethidine, Aminophyllin, Isoproterenol, ether, atropine and epinephrine may be used to overcome bronchospasm.

HISTORY

Mr. M. P. was a 67-year-old Russian with a 3-month history of persistent cough and copious blood-tinged sputum. He smoked very little but drank heavily. There was no history of asthma, bronchitis or pneumonia, but examination of his chest showed a moderate degree of emphysema with some basal rales. A chest X-ray disclosed parenchymal infiltration with cavitation involving the superior segment of the lower left lobe. In view of the diagnosis of lung carcinoma with abscess, surgery recommended a thoracotomy and possible pneumonectomy.

PREMEDICATION

Atropine 0.4 mg. and Pethidine 75 mg. were given one hour preoperatively. On arrival in the operating room, he was alert, breathing comfortably with a systolic blood pressure 140 mm. Hg and a pulse rate of 84.

ANAESTHETIC COURSE

Following oxygenation, induction was accomplished by thiopentone 450 mg. and succinylcholine 60 mg. After spraying the throat with 4 per cent lidocaine, a No. 10 cuffed endotracheal tube was passed easily and inflated. Auscultation indicated satisfactory aeration of both lungs. One litre of N_2O and one litre of O_2 were used in the circle of a Boyle's machine. D-tubocurare 15 mg. was injected into the intravenous tubing. Respiration was maintained by a Jefferson respirator at a rate of 20 per minute with a positive pressure of 18 cm. H_2O and a negative pressure of 8cm. H_2O.

When the patient was postured on his right side, breath sounds became coarse and rhonchi were heard throughout the chest. Suction yielded very little sputum. As he had a swallowing reflex, he was given Pethidine 20 mg. followed shortly by thiopentone 100 mg., d-tubocurare 6 mg. and finally by Aminophyllin 50 mg. Respiration, though noisy, seemed adequate. Pulse, blood pressure and the E.C.G. tracing were normal and the operation proceeded.

[1]Clinical Assistant, Department of Anaesthesia, Montreal General Hospital.

Cyclopropane, 200 cc. per minute, was added to the gas mixture when the surgeon finished with the cautery. The negative phase of the respirator was turned off when the pleura was opened. Aminophyllin, thiopentone and Pethidine were injected at intervals. The rate of the respirator was reduced to 14 per minute to adapt to the long expiratory phase of the patient's respiration. The addition of ether made ventilation easier but the breath sounds continued to be noisy.

During the first two hours, blood pressure, pulse and E.C.G. remained normal. A few ventricular extrasystoles appeared with incision of the pericardium and responded to 1 per cent Procaine topically. The surgeon complained of over-distension of the lung; so the positive pressure was reduced. This decreased oxygenation so markedly that the pressure was increased again. At this time it was decided to withdraw the endotracheal tube slightly in case it might be causing reflex stimulation at the carina. The airway was checked afterwards and found to be patent. At this time the E.C.G. showed a multofocal arrhythmia and the surgeon reported the onset of asystole. Simultaneously a bronchospasm developed which was so severe that no air returned from the lungs and they became grossly distended. Use of the negative phase on the respirator seemed to decrease the inflation but was not continued. Asystole occurred several times and responded to massage each time. A recordable blood pressure was not obtained during the period of acute pulmonary distension. The interval of severe hypoxia lasted from ten to fifteen minutes. Finally after giving Aminophyllin 150 mg. intravenously and injecting the hilar area with procaine 1 per cent, it became possible to ventilate the lungs. Tracheal suction produced asystole again. Responding at once to massage, the heart began to fibrillate but this stopped with further massage. The systolic blood pressure rose sharply to 140 mm. Hg owing to the entrance of trapped Methoxamine into the circulation.

The surgeon proceeded with the pneumonectomy and the chest was closed one and a half hours later. During this time the patient received O_2 by manually controlled intermittent positive pressure with the addition of N_2O and cyclopropane for chest closure. The blood pressure fell briefly on two occasions because of interference with the position of the heart by the assistants. Normal cardiac rhythm returned before the end of the operation.

Postoperative Course

Neither spontaneous respiration nor consciousness returned at the end of the operation. Tracheal suction produced a slight response. Neostigmine and nikethamide were ineffective. Finally the use of carbon dioxide (7 per cent) produced respiration with no pause between phases.

In the recovery room the patient required a continuous drip with Phenylephrine to maintain his blood pressure for the the first two hours. The E.C.G. tracing was normal. When stimulated, he moved both arms and his right leg. He had received a total of 2,500 cc. of blood to control his pressure with an estimated blood loss of 1,200 cc.

Two hours later, breathing became more mechanical. Examination of the optic fundi revealed engorged veins and blurred discs. The injection of 50 cc. of dextrose (50 per cent) produced quieter respiration and his response to stimulation increased. Chest X-ray showed considerable mediastinal shift and 150 cc. of air were added to the left pneumothorax. Pulmonary oedema developed during the next hour and cleared with the use of Aminophyllin 200 mg., Digoxin 0.5 mg. and a phlebotomy of 250 cc. of blood. The E.C.G. tracing, which had recorded ventricular extrasystoles, returned to normal.

During the evening and night he improved to the extent of developing a lash reflex. Next day an E.E.G. showed practically no alpha activity and no response to reflexes. The findings suggested brain-stem damage. He died 48 hours after the operation and unfortunately no autopsy report was obtained.

Summary

A case report of bronchospasm during a pneumonectomy has been presented. The difficulty in ventilation was due to spasm of the bronchial tree, and fixation of the chest wall was not a factor. The gross inflation of the lungs did not respond to treatment before there was severe cerebral anoxia. It is believed that this was the cause of death.

Résumé

Au cours d'une pneumonectomie pour carcinôme chez un vieillard de 67 ans, il est apparu un spasme bronchique. Les manipulations dans le thorax ont entraîné une arythmie ventriculaire qui a dégénéré en asystolie. A ce moment-là, le spasme bronchique est devenu tellement prononcé que l'air ne sortait plus des poumons qui sont devenus distendus à l'excès. Le cœur a répondu rapidement au massage et la distension pulmonaire a persisté s'accompagnant d'une hypoxie aiguë qui a duré de 10 à 15 minutes. On n'a réussi à ventiler le malade qu'après avoir pratiqué une injection intraveineuse d'aminophylline et une injection autour du hile des poumons de procaïne à 1%. Une heure et demie plus tard, la pneumonectomie était terminée. La respiration spontanée est réapparue avec l'emploi de gaz carbonique à 7%, mais le malade n'a pas repris conscience. Un électroencéphalogramme, pratiqué le lendemain, a montré des lésions cérébrales et le malade est mort 48 heures après l'opération.

BOOK REVIEWS

ACTA ANAESTHESIOLOGICA SCANDINAVICA. Aarhus, Denmark: Universitetsforlaget i Aarhus. Annual subscription, 40 Danish Kroner.

This first volume of a new journal in the specialty of anaesthesia is of an excellence which augurs well for its future. Published in Denmark, but in the English language, both the format and quality of the publication are most excellent. The *Journal* is edited by Dr. Eric Nilsson of Lund who has the assistance of a number of distinguished collaborators in the Scandinavian countries. The first volume contains five excellent papers, the contents being: Changes in Blood Volume in Induced Hypothermia, by Bertil Lofstrom; The Effect of Some Curarizing Drugs in Unanaesthetized Man, I, by Henning Poulsen and Willy Hougs; Enophthalmus Elicited by Succinylcholine, by Ake Bjork, Matts Halldin and Ake Wahlin; Sleep Reinduced by Cortisone and Glucose in Patients Intoxicated with Barbiturates and Related Drugs, by K. G. Dhuner and P. Nordqvist; and The Fate of Muscle Relaxants in Man, by Francis F. Foldes.

R.A.G.

BRITISH MEDICAL BULLETIN, January 1958.

The formation of a separate Faculty of Anaesthetists, by the Royal College of Surgeons of England, served as a considerable stimulus to post-graduate teaching and research in that country.

From time to time, symposia on various relevant subjects have been organized —some as all day sessions at the College and others appearing only in print. The latest of these appears in the *British Medical Bulletin*, under the auspices of the British Council. As with the other symposia mentioned, the authors are all nationally known figures. A variety of subjects is handled, striking a happy balance between clinical anaesthesia and basic science. Of the former, the articles on "Obstetrical Anaesthesia" (Dr. Selwyn Crawford), "Respiratory Inadequacy" (Dr. Ronald Woolmer) and "Deaths and Anaesthesia" (Association of Anaesthetists Committee) are of particular interest.

The review articles on basic science topics are of perhaps even greater interest, especially "CO_2 Haemostasis in Anaesthesia" by Professor Pask, "Biochemical Disturbances and Anaesthesia" by Drs. J. D. Robertson and S. C. Frazer and "Electrographic Monitoring of Anaesthesia" by Dr. B. D. Wyke.

Many other articles are worthy of mention and, certainly, this symposium merits the attention of us all.

H.B.F.

OBITUARY

Charles Stewart

Dr. Charles C. Stewart, one of Canada's most senior anaesthetists, died in Montreal on January 19, 1958, aged 70.

Dr. Stewart was born in Scotland, came to Canada as a young man, and commenced the study of medicine at McGill in 1912. Like many other medical students of that era, he enlisted in 1915 in the ranks of No. 3 McGill General Hospital, and soon was sent to France. He was promoted to the rank of Corporal, was instructed how to "pour ether," and he soon was spending his full time as an anaesthetist. In 1918 he returned to McGill, graduated in 1921; and after internship at the Montreal General Hospital he started the practice of anaesthesia. In 1928 he succeeded the late Dr. Hepburn as anaesthetist-in-chief at the Montreal General Hospital and continued in that post until his retirement in 1954. After this he served at the Reddy Memorial Hospital, Montreal, but was incapacitated by a stroke early last summer.

Dr. Stewart was an enthusiastic clinical teacher, and long before there was any organized university teaching of anaesthesia he trained many anaesthetists on an apprenticeship basis. These doctors now recall Dr. Stewart's guidance and friendship with great appreciation.

When the Department of Anaesthesia was organized at McGill in 1946, Dr. Stewart was named an Assistant Professor, and he took an active part in the teaching programme until he retired from the Montreal General Hospital. He was an original member of the Anesthetists' Travel Club, organized by Dr. John Lundy and Dr. Ralph Waters in 1929, now reorganized as the Academy of Anesthesiology. He received the Diploma in Anaesthetics of the Royal College of Surgeons of England, was certified in anaesthesia by the Royal College of Physicians and Surgeons of Canada, and by the College of Physicians and Surgeons of Quebec. He was a member of the Canadian Anaesthetists' Society from the time of its founding in 1943.

Dr. Stewart is survived by his wife, the former Lillian Adair of Montreal, and by two sons and one daughter. We extend to Mrs. Stewart, and the members of her family, the heartfelt sympathy of all Canadian anaesthetists.

CANADIAN ANAESTHETISTS' MUTUAL ACCUMULATING FUND LIMITED

FOLLOWING a preliminary canvas of the opinion of members of the Society, the Annual General Meeting of the Canadian Anaesthetists' Society in June, 1957, authorized the incorporation of an open-end mutual investment fund to be known as Canadian Anaesthetists' Mutual Accumulating Fund. Letters patent for the Fund were issued by the Secretary of State for Canada on September 13, 1957.

In order to keep sales cost of shares of the Fund as low as possible, the Directors determined that the Fund should apply for licence to issue its own shares in each of the provinces of Canada except Prince Edward Island, where the number of members of the Canadian Anaesthetists' Society did not warrant the expense involved in securing such a licence. This process required a considerable period of time, and the delay in issuing the licence was extremely prolonged in some provinces. As a result there was a corresponding delay in the availability of shares in the Fund to residents of some of the provinces.

Unfortunately there appears to be confusion in the minds of some members of the Society as to the nature of the Canadian Anaesthetists' Mutual Accumulating Fund Limited. This Fund is not a pension plan registrable for income tax deferment. In registered plans the contributions are "locked in" until taken as an annuity, and the value represented by such funds may not be pledged as security to obtain credit. When the payments are received from a "registered" plan, the whole amount received is taxable, including any portion which may represent capital appreciation of the sums invested.

The Class "A" shares of Canadian Anaesthetists' Mutual Accumulating Fund are redeemable on short notice on application to the Fund, at the net asset value of the shares at the time of redemption, and only that portion of the sum received at redemption which is represented by dividends paid into the subscriber's account by the Fund in the current year is taxable under current legislation, while even this amount is subject to the 20 per cent reduction before taxes which is allowed on dividends of taxable Canadian corporations.

For the shareholder the Fund provides the investment of *even small amounts of personal capital* in a wide range of first-class securities representing all areas of the national economy, under expert investment management. The provision of a convenient monthly savings plan for the purchase of shares provides for automatic growth of personal holdings, while the re-investment of dividends provides for compounding in the account of the individual investor. Since the individual shareholder in the fund pays the income tax in each taxation year on the dividends credited by the Fund to his account, the whole of the sum accruing from the eventual redemption of shares will be income tax free, under present legislation.

The objective of the Directors and Managers of the Fund is to produce the maximum in long-term capital growth. Each security added to the approved list is carefully scrutinized with this objective in mind. No speculative securities are

included in the approved list. In the short period of its existence the net asset value of the shares of the Fund has shown most satisfactory increase.

R. A. Gordon, M.D.
President,
Canadian Anaesthetists' Mutual
Accumulating Fund Limited

178 St. George Street,
Toronto 5, Ontario.

MEETINGS

ONTARIO MEDICAL ASSOCIATION, SECTION OF ANAESTHESIA
Toronto, Ontario
May 15, 1958

CANADIAN MEDICAL ASSOCIATION, ANNUAL MEETING
Halifax, Nova Scotia
June 16–20, 1958

CANADIAN ANAESTHETISTS' SOCIETY ANNUAL MEETING
Seigniory Club, Montebello, P.Q.
June 23, 24, 25, 1958

ONTARIO DIVISION, CANADIAN ANAESTHETISTS' SOCIETY
London, Ontario
September 27, 1958

AMERICAN SOCIETY OF ANESTHESIOLOGISTS, ANNUAL MEETING
Pittsburgh, Pa.
October 20–24, 1958

WORLD FEDERATION OF SOCIETIES OF ANAESTHESIOLOGISTS SECOND WORLD CONGRESS OF ANAESTHESIOLOGISTS
Toronto, Canada
September 4–10, 1960

CANADIAN ANAESTHETISTS' SOCIETY ANNUAL MEETING

SEIGNIORY CLUB, P.Q., JUNE 23, 24, 25, 1958

PROGRAMME

Monday, June 23

9.00 A.M. Registration and visiting exhibits.

2.00 P.M. Dr. J. Gordon Robson, "Some Observations on Regurgitation and Vomiting during Anaesthesia"

2.30 P.M. Dr. P. Bromage, "Factors Influencing Pulmonary Compliance in Anaesthesia"

3.00 P.M. Break to visit exhibits

3.30 P.M. Dr. Allen B. Dobkin, "The Effect of Anticholinergic Drugs on the Cardiac Vagus"

4.00 P.M. Dr. R. A. Millar, "Studies with Haemorrhagic Hypotension"

Tuesday, June 24

9.00 A.M. Dr. Eva M. Kavan, "Electroencephalographic and Electrocardiographic Patterns during Intracardiac Surgery using the Cardio-pulmonary Bypass: A Comparison of the Effect of Different Anaesthetic Agents"

9.30 A.M. Dr. D. LeRoy Crandell, "The Role of the Anaesthesiologist in the Management of Severe Systemic Tetanus"

10.00 A.M. Break for viewing exhibits

10.30 A.M. Annual General Meeting

2.00 P.M. Dr. Fernando Hudon and Dr. André Jacques, "Fluothane-Ether Mixture"

2.30 P.M. Dr. I. M. MacKay, "A Clinical and Laboratory Evaluation of Four Fluothane Vaporizers"

3.00 P.M. Break to visit exhibits

3.30 P.M. Dr. Gordon M. Wyant, "Serial Cardiac Output Determinations during Fluothane Anaesthesia"

4.00 P.M. Dr. R. G. B. Gilbert, "Second Thoughts on Fluothane in Neurosurgery"

7.00 P.M. Formal dinner

Wednesday, June 25

9.00 A.M. Dr. Eric Webb, "Ten Years of Group Practice"

9.30 A.M. Dr. M. Keéri-Szántó and Dr. J. Labarre, "Serum Protein Changes in Thiopental-Nitrous Oxide Anaesthesia"

10.00 A.M. Break to visit exhibits

10.30 A.M. Dr. H. B. Graves, "Shock in Obstetrics"

11.00 A.M. Dr. J. Rosales and Dr. T. Davenport, "Difficult Endotracheal Intubation of Infants and Children"

2.00 P.M. Reports of Work in Progress.
Dr. R. G. B. Gilbert, "Preliminary Studies with a New Short Acting Intravenous Anaesthetic Agent"
2.10 P.M. Dr. J. Beldavs, "Intramuscular Relaxant in Infants"
2.20 P.M. Dr. G. Fortin and Dr. W. Tremblay, "The Short-Needle Technique in Brachial Plexus Block"
2.30 P.M. Dr. L. Lamoureux and Dr. J. Lafleur, "The Pudendal Block Technique for Both Sexes: Value, Advantages and Disadvantages"
2.40 P.M. Dr. Marjorie Bennett, "Preliminary Report on the Use of G-29505"
2.50 P.M. Dr. J. J. Carroll, "The Anti-hypnotic Effect of Ritalin"
3.00 P.M. Break to visit exhibits
3.30 P.M. Dr. S. M. Campbell, "Evaluation of Pipadone"
3.40 P.M. Dr. Ian Purkis, "The Potentiation of Obstetrical Analgesia by Tranquilisers"
3.50 P.M. Dr. R. A. Millar, "Plasma Catechol Amine Levels"
4.00 P.M. Dr. G. I. McGillvray, "Comparative Study of Histamine Release by Various Opiates"
4.10 P.M. Dr. T. Davenport, "Investigation of Cardiovascular Effects of Fluothane"
4.20 P.M. Dr. Rosario Denis, "Preliminary Study on the Problem of Alkalosis in Anaesthesia"

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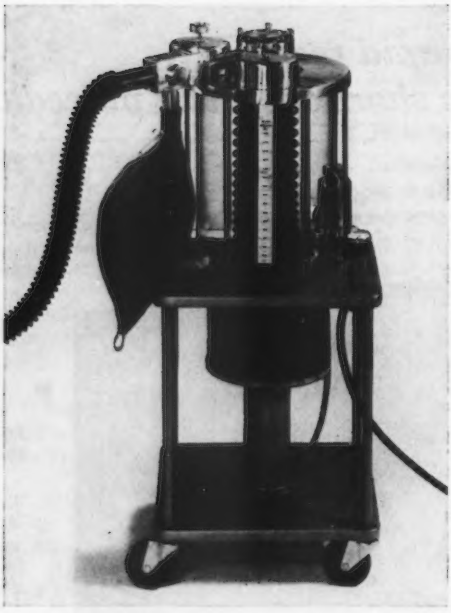

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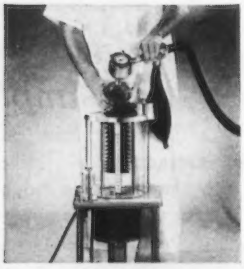

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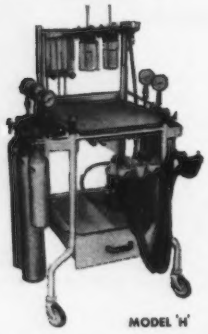

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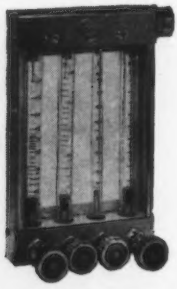

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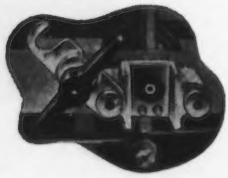

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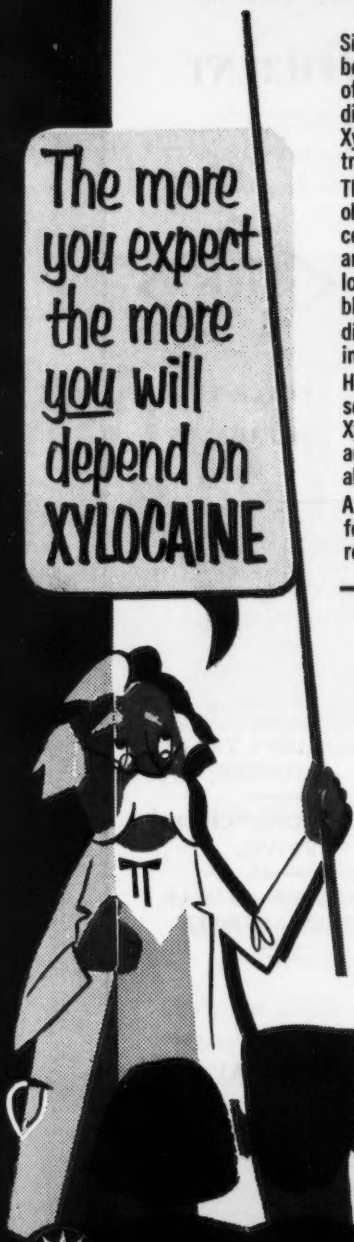

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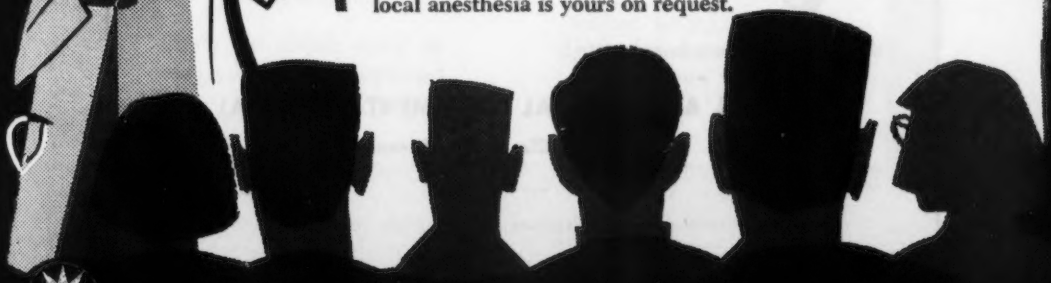

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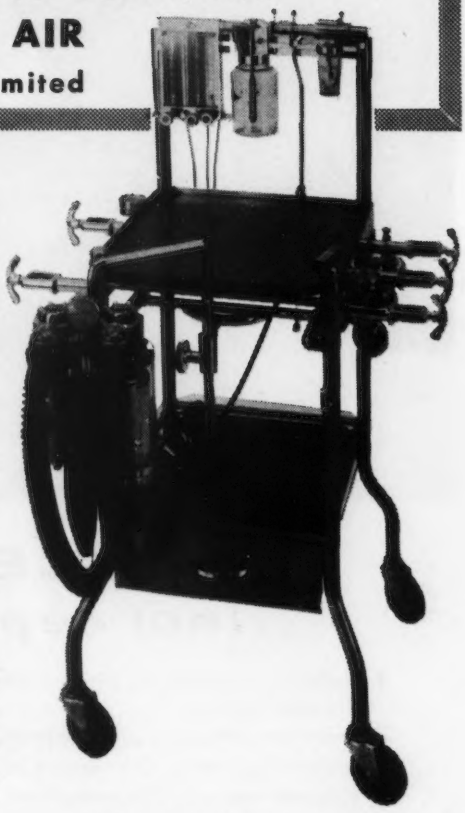

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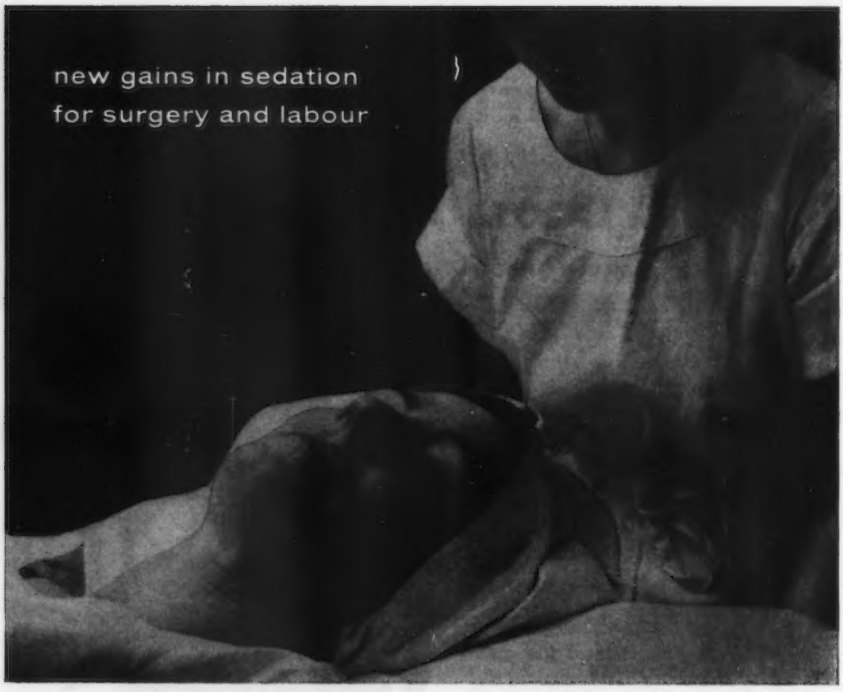

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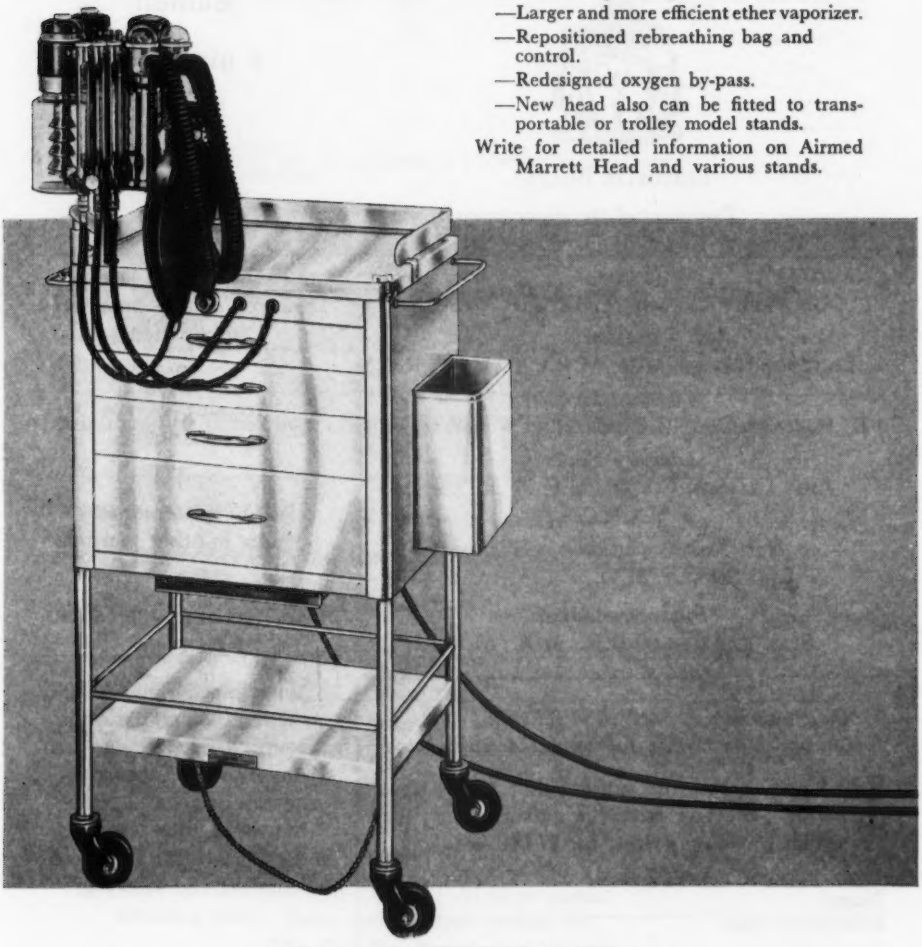

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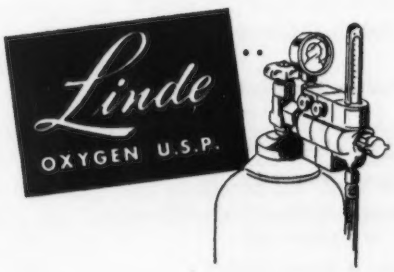

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